Clinical Cardiopulmonary Physiology

Editorial Board

Clinical
CARDIOPULMONARY PHYSIOLOGY

Second Edition, Revised and Enlarged

Sponsored By The

American College of Chest Physicians



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Foreword

CARDIOPULMONARY physiology has contributed richly to our present knowledge of clinical and fundamental medicine. Notable advances include the development of technics and apparatus for the evaluation of impaired function. It has been possible, as a result, to undertake with remarkable value and safety the surgical treatment of congenital heart disease, anomalies of the heart and unresolved pulmonary processes, and to utilize dynamic medical procedures for the relief of long-continued and disabling manifestations. Interestingly, the basic principles have been carried far beyond the experimental laboratory—to outer space and down into the sea where survival calls for timely and exacting physiologic support.

The most significant contributions have occurred coincidentally with the decreasing frequency of acute and chronic infections. For example, there has been a striking reduction of so-called rheumatic heart disease, diphtheria, syphilis, tuberculosis, pneumonia and suppurative processes of the lungs and pleural cavity. Preventive medicine and chemotherapy hold their rightful claim for controlling these dread infections, but the newly won laurels are overshadowed by the rising incidence of degenerative diseases of the heart and lungs, as would be expected after the fifth and sixth decades of life. Indeed, because of his escape from the killing infections, man is living longer, only to fall prey to conditions that favor progressive physiologic disability. Examples include coronary heart disease, impairment of the pulmonary circulation, emphysema, fibrosis and cystic disease of the lung. Adding complexity is cancer, superimposed on a physiologic condition characterized in itself as a serious problem for survival. Thus, a fatal termination in the former may be accelerated by the degenerative process, especially in cases requiring extensive resection, lobectomy and pneumonectomy. In such situations, there may well be the question: Is it possible for the remaining lung tissue to assume an additional burden of respiration?

It is realized that the medical history, the physical examination, x-rays and the blood determinations for the evaluation of actual or potential disability are subject to limitations. And increasingly the general practitioner, surgeon and consultant are turning to the physiologic laboratory for critical information. For example, the barrel-shaped chest, once regarded as characteristic of emphysema, may be found with detailed study to be essentially normal, physiologically, massive nodulations in the lungs of coal miners, often associated with advanced and disabling pneumoconiosis, are sometimes less disturbing functionally than fine and more scattered processes, catheterization in valvular heart disease may reveal the exact nature of the circulatory disturbance. Accordingly, the boundaries for radical treatment of cardiac and pulmonary diseases are no longer limited to speculation and empirical treatment. It is significant that the symptoms and physical signs have assumed even greater importance to the clinician through physiologic appraisal, and, in turn, clinical data have become more intriguing and interesting to the physiologist.

The scientific literature is the vehicle of original thought and discovery. It is the linguistic medium that enables scientists the world around to communicate to one another the observations gained from basic, exacting research. Yet, in this land of scientific plenty and conscientious reporting, there is difficulty of dissemination into the channels of medical practice. The problems are multiple. Physicians generally are laboring under the pressures of great responsibility, with limited opportunity to delve into the

mountainous backlog of scientific literature Reading may be difficult, because of the sort of jargon commonly used in scientific reporting—easily understood by investigators but often confusing to those separated from fundamental medicine How is the busy physician able to weed out and summarize the countless articles for his particular use? How can he interpret critically the complicated tables, graphs and formulas in the light of varied concepts and the very technical literature?

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sina, who, in 1661 in his correspondence with Giovanni Borelli (1608–1679) of Pisa, described the vesicular structure of the lung and demonstrated the branching of the trachea into the bronchial tree and its termination in the alveoli of the lungs. In his second letter, Malpighi reported his histologic demonstration of the capillary union between arteries and veins.

Eight years later (1669), another important physiologic contribution pertaining to the cardiopulmonary system was reported by Richard Lower (1631–1691), of Cornwall. He injected dark venous blood into insufflated lungs, observed its subsequent red color and concluded that the change resulted from the blood having absorbed some of the air passing through the lungs. He also demonstrated anastomoses between coronary arteries by experimentally injecting one artery from another. Lower investigated the contractions of the heart and concluded that the heart was basically a muscle.

Another closely related experiment was conducted by John Mayow (1643–1679), also of Cornwall, and the results were published in 1674. While working with a gas which he had obtained from niter and which he called "nitroaerial spirit," observed that the dark venous blood became red when it was placed in contact with the gas. Mayow was unaware of the fact that he nearly discovered oxygen. That important discovery belongs to Priestley and Scheele (1771), and to Lavoisier (1775).

An early experiment and one of the first using a primitive plethysmograph was conducted by Jan Swammerdam (1637–1680) of Holland. He studied the movements of the heart, lungs and muscles and concluded that a muscle does not increase its bulk during contraction. Swammerdam also injected wax into blood vessels in order to observe their finer tributaries and anastomoses.

Also concerned with the physiology of muscles was Giorgio Baglivi (1668–1706) of Rome. He was the first to identify and distinguish the differences between smooth and striated muscle (1700). In his experiments, he also severed the vagi in the neck of the dog and found that the animal was unable to bark and developed dyspnea and vomiting.

Five years later (1705), Raymond Vieussens (1641–1716) of Montpellier performed important experiments dealing with the blood supply of the heart. He described the course of the coronary arteries, the valve of the large coronary vein and the coronary sinus. Vieussens suggested the idea that the coronary vessels have direct communication with the chambers of the heart, a fact proven by a contemporary three years later. He also insisted that cyanosis was not necessarily the result of admixture of venous and arterial blood and thus conceived the modern idea of anoxia.

In 1708, Adam Christianus Thebesius (1686–1732), who was aware of Vieussens' work, injected materials into the coronary vessels and observed their passage into the chambers of the heart by way of small orifices in the endocardium. Even today this sinusoidal circulation is known as the "thebesian system" which plays an important role in the venous drainage of the heart.

Among other observations pertaining to the heart, Francesco Ippolito Albertini (1662–1738) of Bologna brought forth his concepts regarding certain phases of heart failure (1726). He discussed pulmonary edema and concluded that it occurred as the result of impaired circulation in and through the heart. Albertini ascribed dyspnea to congestion of the lungs and stated that its progression results in hydrothorax. He also differentiated pulmonary congestion and pulmonary edema from hydrothorax.

The first attempts to measure blood pressure were made by a scientific-minded clergyman, Stephen Hales (1677–1761), of Beckesbourne and Teddington in 1733. While his hydrostatic methods were crude in comparison to modern procedures, his work nevertheless opened the portals for numerous subsequent experiments. Hales used horses, sheep and dogs and attempted to measure blood pressure by inserting long glass tubes into an artery and record the height attained by the column of blood. He also studied the pulse by means of the sphygmoscope, injected wax into the cardiac chambers and the aorta to determine their capacity and these values were used in his computations. He estimated the blood pressure in man to be

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The History of Cardiovascular Physiology

By FREDRICK A WILLIUS, M D.

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[Ph]YSIOLOGY OF THE HEART AND CIRCULATION

MEDICAL antiquity reveals but few phys[-]iologic contributions dealing with the [car]diovascular system The correct and com[ple]te knowledge of the structure of the human [bod]y was lacking and attempts to ascribe func[tio]n to known components were wholly con[jec]ture and usually erroneous For instance, [H]ippocrates (460–370 B C) of Cos (ancient [G]reece) believed that the arteries contained [air] while the veins were filled with blood This [err]oneous conclusion, widely accepted at the [tim]e, was undoubtedly based on the fact that [th]e arteries are empty after death

The greatest deterrent to physiologic and [an]atomic progress was the fallacious teaching [of] Claudius Galen (138–201 A D) of Perga[m]on, Asia Minor. He insisted that the blood [wa]s formed in the liver from ingested food and [th]en transported by the veins to the right side [of] the heart and by a mechanism of ebb and [flo]w back to the liver He then postulated that [th]e blood was distributed to all parts of the [bo]dy by other veins A small residue of blood [re]mained in the right chambers of the heart [w]hich eventually gained access to the left [ch]ambers through "invisible pores" in the [in]terventricular septum It is obvious that his [in]correct physiologic reasoning was based on [fa]ulty anatomic findings. It is amazing that [G]alen's teachings were accepted for nearly [fo]urteen and one-half centuries.

It was not until 1628 when William Harvey [(1]578–1657) of Folkestone published his monu[me]ntal work, *Exercitatio Anatomica de Motu [C]ordis et Sanguinis in Animalibus*, that signifi[ca]nt progress in physiologic contributions be[ca]me apparent. This was the first correct [an]atomic and physiologic demonstration of the [he]art and the circulation

However, as early as the thirteenth century, [I]bn an-Nafis (circa 1210–1288), dean of the Mansoury Hospital in Cairo, was the first to describe accurately the pulmonary circulation. His work appeared in *Commentary on Anatomy* and the circulation was clearly described far more completely than the general physiologic principles of respiration Ibn an-Nafis utilized logic and speculation in deducing the general scheme of the pulmonary circulation The alveoli of the lungs were mentioned (first definitely demonstrated by Malpighi in 1660) and also the statement that the heart was nourished by its own arteries, thus implying the existence of the coronary circulation

Approximately a century and three-quarters later (circa 1546 or 1553), Michael Servetus, the Martyr (1509–1553), of Villanueva de Sigena, Spain, also described the pulmonary circulation in a religious treatise, "Restitutio Christianismi " No proof exists that he was aware of Ibn an-Nafis' earlier contribution and it was not until 1924 when a young Egyptian physician, Muhyi ad-Din at-Tatāwi, rediscovered Ibn an-Nafis' work

Other early investigators of the systemic and pulmonary circulations were Matteo Realdo Colombo (Columbus), 1516?–1559, of Cremona and Andrea Cesalpino (1519 or 1524–1603) of Arezzo

While Harvey postulated the existence of communications between the arteries and veins as a necessary feature of the circulation of blood, he was unable to actually demonstrate them because no method of magnification was available to him The history of magnification and the development of the microscope is a fascinating chapter in medical history.*

It was Marcello Malpighi (1628–1694), professor of anatomy at Bologna, Pisa and Mes-

* See HENKER, O Microscope *In* The Encyclopedia Brittanica, ed 11, Cambridge, England, University Press, 1911, also VAN LEEUWENHOEK Antony Ontledingen en Ontdekkingen, Leyden, 1696.

bridge conducted interesting experiments with reference to the rhythmicity of the heart. In 1859, Foster reported that any portion of the heart separated from the rest will beat rhythmically. Foster also showed that the heart without its ganglia continues to beat in a normal manner. This led him to conclude that rhythmicity is a specific and inherent quality of heart muscle. Adolph Fick (1829-1901) established his principle for determining cardiac output. This principle has been an excellent tool for studying the physiology of the heart both in normal and abnormal states.

The first physiologic laboratory in the United States was founded by Henry Pickering Bowditch (1840-1911) of Boston. He was interested in the physiology of muscles, especially of heart muscle. By direct stimulation of the exposed myocardium by direct electrical stimulation of uniform frequency and intensity, he found that the first few contractions were slightly diminished, but after the initial diminution, the contractions increased with remarkable regularity. This gradual increase in the degree of muscular shortening with a uniform stimulus led him to designate this reaction "treppe" or staircase phenomenon. Following this period, the contractions steadily diminished until muscular fatigue occurred, and no further response to stimulation was evident. Bowditch then concluded that the heart liberated all its available energy at each contraction and that cardiac contraction depends on the amount of energy stored in the muscle and that contraction is always maximal. This phenomenon became known as the "all-or-none" law of Bowditch.

The pathologic physiology of pulmonary edema was investigated by William Henry Welch (1850-1934) of New York and Baltimore, and his results were published in 1878. He concluded that edema of the lungs occurred when the outflow of blood from the left ventricle was reduced, as in left ventricular failure. The blood continuing to reach the lungs from the right ventricle, still functioning adequately, results in increased pressure within the pulmonary circulation. The result of these circumstances eventuates in stasis and seepage of fluid and cells into the alveoli of the lungs. The rapid occurrence of these events together with the remarkable permeability of the lung capillaries encourages the development of pulmonary edema.

Maude Abbott (1869-1940) stimulated a renewed interest in congenital heart disease when she published her treatise in 1908. This in turn led Helen Taussig (1898-) to her clinical studies in congenital heart disease and the resulting development by Alfred Blalock (1899-) of his "blue baby" operation. This began the great era of congenital heart surgery.

One of England's great physiologists, Ernest Henry Starling (1866-1927) of London, in collaboration with S. W. Patterson of London and H. Piper of Berlin, formulated his famous "law of the heart" in 1914. This, in brief, is that the heart is able to adjust within limits to the demands of increased work. Carl Wiggers (1883-) through his ingenious methods of instrumentation refined our knowledge of the physiologic processes in the cardiovascular area. In 1929, Werner Forssmann described his method of catheterizing the right heart by his own daring self experimentation. Andre Cournand and Dickinson W. Richards, Jr. applied Forssmann's technic to clinical and physiologic studies which resulted in all three receiving the Nobel Prize in medicine in the year 1956.

Electrophysiology of the Heart

Willem Einthoven (1860-1927) of Leyden is generally considered to be the originator of the science of electrocardiography. While Einthoven's work in this field was outstanding, nearly a century and one-quarter of investigation by others made possible his brilliant contribution. It is important to appreciate the historical sequences that preceded Einthoven's classic publication of 1903.

In the third quarter of the eighteenth century, the eminent Italian physiologist, Luigi Galvani (1737-1798) of Bologna, conducted the first experiments in electrophysiology. When he observed that an electric stimulus applied to the exposed nerve of a frog's leg resulted in contraction of the muscles of that leg, the experiment opened the door for all subsequent studies in electrophysiology.

A large contribution to electrophysiology was made in about 1848 when Johannes S. C.

out 7½ feet (229 cm) according to his system of measurement.

Nearly a century elapsed before other studies concerned with blood pressure determinations were made Jean-Marie Poiseuille (1799–1869), employed the mercury manometer in 1828, as Carl F. W Ludwig (1816–1895) in 1847 Riva-Rocci (1863–1937) made the clinical application of blood pressure determination possible through his development of the "compression method" of determining blood pressure 1891 Harry Goldblatt, American physiologist, established permanent hypertension in dogs by constricting the renal arteries This led increased research into hypertension Many other investigators such as Braun-Menendez of Buenos Aires and Irvine Page of Cleveland have increased our knowledge of the fundamental concepts of hypertension.

Probably the greatest physiologist of the eighteenth century was Albrecht von Haller (1708–1777) of Bern and Gottingen Among many investigative works, one of the most important was his demonstration of the property of muscle irritability and the proof of the automatism of the heart. He thus formulated the basis for the myogenic theory of cardiac activity, which was not definitely pronounced until the following century.

An important experiment dealing with hemodynamics was contributed by Lazaro Spallanzani (1729–1799) of Scandiano in 1777. In addition to studying the role of the heart and circulation from the embryo to the adult, he was the first to demonstrate that the impetus given to the blood by the contraction of the heart was maintained throughout the entire arterial system as far as the smallest capillary.

Related to Spallanzani's contribution was the work of Caleb Hillier Parry (1755–1822) of Bath 39 years later (1816) Among his conclusions (some correct; others incorrect) was the statement that the pulse wave is caused by the impetus given to the blood by systole of the left ventricle.

Investigating the mode of production of the heart sounds, James Hope (1801–1841) of Edinburgh and London conducted interesting experiments in 1831. He examined the hearts of stunned donkeys whose respiration had been artificially sustained After opening the pericardium and observing the pulsating heart, Hope demonstrated that the second sound is caused by the abrupt closure of the aortic and pulmonary valves

An important discovery was made by the Weber brothers in 1845 Ernst Heinrich Weber (1795–1878) of Wittenberg and Leipzig and Eduard Friedrich Weber (1806–1871) proved the cardio-inhibitory action of the vagus At an earlier date, the brothers had measured the velocity of the pulse wave for the first time and later measured and compared the velocity of the blood and lymph corpuscles in the capillaries Much later, 1919, August Krogh of Copenhagen conducted important studies dealing with the physiology of the capillaries, for which he was awarded the Nobel Prize in 1920.

In 1852, Hermann Stannius (1808–1883) of Hamburg applied a ligature at the union of the auricle and the sinus venosus of the frog's heart which caused the heart to cease beating He then applied a second ligature to the auriculoventricular groove which caused the ventricles to beat again This important experiment proved that the ventricles are endowed with the property of initiating their own rhythm in heart block (idioventricular rhythm)

To omit the contributions of the eminent Claude Bernard (1813–1878) of Paris would be unforgivable Among his many talents and contributions, he made certain discoveries pertaining to the cardiovascular system By ingenious experiments (1854), he demonstrated the vasomotor nerves and their functions. Bernard severed the sympathetic nerve of a rabbit and noted an increase of local temperature of the ear in which a decrease of temperature had been expected He was uncertain whether the congestion in the vessels of the rabbit's ear accounted for the rise of temperature He then repeated the experiment after two of the veins supplying the ear had been ligated and the same results were obtained He concluded that the sympathetic nerves control temperature In later experiments, Bernard proved that the sympathetic nerves when stimulated produce vasoconstriction and the chorda tympani, vasodilatation.

Sir Michael Foster (1836–1907) of Cam-

cause of its inertia, produced curves which were not accurate and, therefore, did not truly measure the electrical changes accompanying the heart beats. Karl Wenckebach (1864–1940) contributed to our knowledge of conduction defects as well as to the treatment of atrial fibrillation by the use of quinine and later by the use of quinidine

Finally, Sir Thomas Lewis (1881–1945) of London made many important contributions in this field. Among numerous investigative studies, in 1910, he proved by means of electrocardiography that the cardiac impulse has its origin in the sino-auricular node (node of Keith and Flack)

James B Herrick, an American internist, described the clinical picture of coronary thrombosis in 1912 bringing about the general recognition of this disease

No chapter on the history of cardiovascular physiology would be complete without mentioning the great role of Frank Wilson of Michigan in our fundamental understanding of electrocardiography

It is impossible to include the many modern investigators of electrocardiography in this review

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ciggcr (1779–1857) of the University of lle invented the string galvanometer. This ovation is frequently and mistakenly as-ed to Einthoven. However, until Eintho-'s time, this instrument was not used with rence to the heart

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Anatomy of the Heart: Normal and Pathologic, as Related to Cardiac Function

By THOMAS N JAMES, M D

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Introduction

ALTHOUGH a knowledge of anatomy of the heart is a prerequisite in the considerations of the pathology and physiology, such information has assumed perhaps greatest significance in cardiac surgery Thus, with the birth of cardiac surgery there has been a resurgence of interest in the meticulous descriptions of Vesalius, Vieussens, Spalteholz and others This rediscovery of old facts will be of benefit to all of us.

In the present review of the normal and pathologic anatomy of the heart, emphasis is directed to features that are of particular clinical significance. For example, the section on coronary artery anatomy is expanded because of the clinical interest in coronary disease, the more detailed considerations are omitted due to availability in standard references on gross anatomy [5, 7, 22] It should be mentioned, however, that certain features which currently seem most important may assume lesser roles in the future, owing to advances in medical knowledge

Pericardium

Normal Anatomy

Investment of the heart by the pericardium may be regarded as consisting of two sacs loosely bound to each other by connective tissue The outer fibrous layer of the pericardium anchors the heart in the mediastinum, since it is firmly attached to the diaphragm below, the posterior surface of the sternum anteriorly and the pretracheal layer of the deep cervical fascia above. The inner serous layer of the pericardium serves as a lining membrane for the sac and is normally in contact with the surface of the heart Where the pericardium reflects from the great vessels, the inner serous layer becomes continuous with the epicardium

Pathologic Anatomy

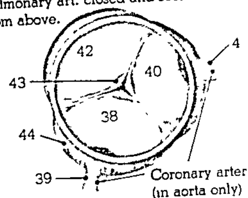
The normal pericardium may be altered by inflammatory processes secondary to infection, as discussed in the chapter on pathophysiology of acute and chronic pericarditis Pericarditis

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FIG 1 —The normal human heart viewed frontally with selective dissection (Reproduced from a series of Heart Drawings, by permission of the American Heart Association and the artist, Leon Schlossberg)

5 Aorta
6 Pulmonary artery
10 Right pulmonary artery
11 Left pulmonary artery
14 Superior vena cava
15 Inferior vena cava
21 R pulmonary vv
22 L pulmonary vv
23 Opening of coronary sinus
24 Interatrial septum
25 Interventricular septum
26 L ventricle
27 R ventricle
29 R atrium
30 Anterior papillary m
31 Fossa ovale
33 Tricuspid valve
35 Pulmonary valve (semilunar)
37 L coronary a
38 Anterior cusp
39 R coronary a
40 L posterior cusp
41 L coronary a
42 R posterior cusp
43 Nodulus semilunaris
44 Sinus of Valsalva
45 Eustachian valve

Semilunar valve of aorta and pulmonary art. closed and seen from above.



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Tricuspid valve closed seen from right atrium

Fig 1 —The normal human heart viewed frontally with selective dissection (*for legend, see facing page*)

Mitral valve closed seen from left atri

proceeds to fibrous thickening and eventually calcification; during the inflammation, effusion sometimes accumulates in the pericardial sac and becomes sufficient to produce cardiac tamponade

Blood in the pericardial sac, such as may follow ruptured myocardial infarction or penetrating trauma, also can cause cardiac tamponade. The remote effect of hemopericardium is somewhat uncertain; it may result in adhesive or constrictive pericarditis The condition is important in view of recent surgical and diagnostic procedures which are uniformly associated with production of a varying degree of hemopericardium.

Myocardium

Normal Anatomy

It is useful to think of the normal four-chambered human heart as functionally one chamber (the left ventricle) with three accessory chambers, participating physiologically (Fig. 1). Both atria, which act as collecting chambers on their respective sides, and the right ventricle, which assists in propulsion of blood into the lungs, possess thin myocardial walls. The only thick myocardium is that of the left ventricle and interventricular septum, which together form a hollow cone of strong muscle. The base of this cone is directed posteriorly, and to the right superiorly; the apex points in the opposite direction to form the apex of the heart. The cone is composed of intricately arranged spiral layers of muscle which interweave with each other; with contraction there is a twisting or wringing of the left ventricle, closing the cavity and propelling the blood into the aorta. The inner third of the left ventricular myocardium is irregular owing to muscular trabeculations The wall of the left ventricle is about two to three times the thickness of the right ventricle. Contraction of the left ventricle probably assists systolic contraction of the right ventricle by pulling muscle bundles attached at the septum of the latter chamber.

Muscle in the right ventricular myocardium is principally in the form of trabeculations, with only the outer millimeter or two consisting of solid muscle. This chamber is in the shape of a tetrahedron with its triangular base lying on the diaphragm and its apex forming the pulmonary conus. Its capacity is 80 to 90 cc , the same as that of the left ventricle.

Papillary muscles project into the cavity of both the right and the left ventricles, with attachments at their apices to chordae tendineae Their function is discussed in the section on cardiac valves In the right ventricle there is only one large papillary muscle, arising from the junction of the anterior free wall with the septum; there is a smaller papillary muscle in the outflow tract of the right ventricle The diaphragmatic wall of the right ventricle gives rise to a variable number of thin papillary muscles. In the left ventricle the papillary muscles are more distinct and constant, two in number, both larger than those in the right ventricle They are located on the anterior and posterior walls of the left ventricle, chordae tendineae from each of these papillae connect with both leaflets of the mitral valve

On cross section near the middle of the ventricles the interventricular septum can be seen normally to bulge to the right, thereby completing a circle with the free walls of the left ventricle (Fig 2) Viewed from the front in its anatomic position, the septum curves convexly into the right ventricle, both in a base-to-apex direction as well as anteroposteriorly, in addition, it spirals from left to right as it descends from the base to the apex of the heart Along its junction with the interatrial septum (a fibrous raphé) it tapers to form a sharp muscular crest; near the midportion of this crest there is a membranous section which represents the last portion of the interventricular septum to form in the fetus, the commonest site for septal defects between the ventricles Externally, the septum is bounded externally by the interventricular sulci, (anteriorly and posteriorly)

The interatrial septum contains relatively little myocardium Viewed from above it assumes the stem of a Y, with the limbs of the Y corresponding to the right and left atrial walls adjacent to the aorta and main pulmonary artery (Fig 3).

The right atrium forms the principal component of the right border of the heart in ana-

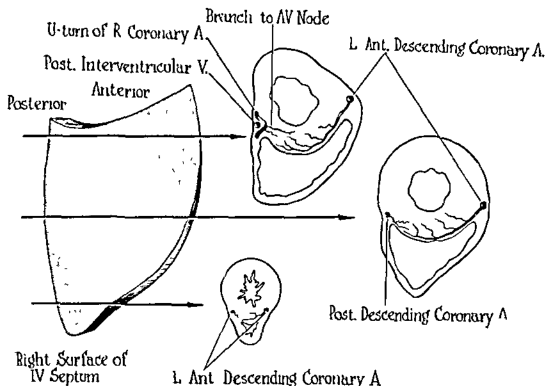


FIG 2 —Schematic representation of the contours of the septum and of cross sections through the ventricles at three levels (Courtesy of James and Burch [11])

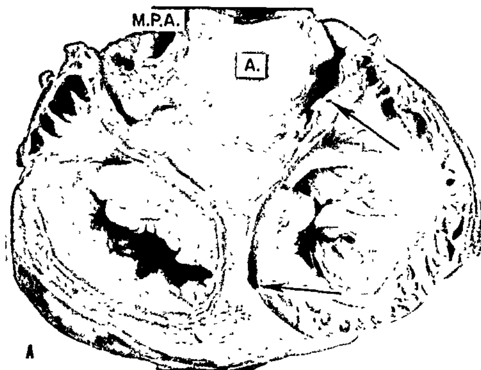


FIG 3 —(A) View of a normal human heart from the top, the upper portions of both atria have been removed Note the "Y" formed by the interatrial septum and the anteromedial wall of each atrium The tricuspid valve is on the right and the mitral valve on the left The main pulmonary artery (M P.A) has been severed flush with the ventricle A is aorta The lower arrow points to the *semilunar single thebesian valve at the entrance of the coronary sinus into* the right atrium The upper arrow indicates the transected ramus ostii cavae superioris in this heart, having arisen from the right coronary artery As is frequently the case, this latter vessel is the only major atrial artery in this heart

tomic position, with the superior vena cava entering at the top and the inferior vena cava from below and behind (FIG. 4). The tricuspid valve opens into the right ventricle in an almost straight lateral direction toward the left The atrial appendage projects toward the base of the pulmonary artery, covering the proximal right coronary artery. The wall is thin, with trabeculated myocardium in the appendage and the lateral half of the atrium, the medial half of the atrium is the intercaval sinus venarum, which is principally a smooth thin sheet of myocardium.

From an anterior view of the heart in anatomic position, the only portion of the left atrium visualized is the appendage, which projects toward the left side of the base of the main pulmonary artery and covers the proximal left coronary artery including its bifurcation. The body of the left atrium is in the back of the heart with the four pulmonary veins entering the area in an anterior direction; the mitral valve opens into the left ventricle, directed toward the apex of the heart. The left atrial myocardium is thicker than the right atrium and is not trabeculated except in the appendage.

Pathologic Anatomy

Most diseases of the myocardium are congenital, metabolic, secondary to coronary atherosclerosis or associated with systemic or pulmonary hypertension. Each of these processes is discussed elsewhere Hypertrophy or degeneration of the myocardium can occur without demonstrable cause.

ENDOCARDIUM

Normal Anatomy

Lining the entire heart, including its valves, is simple squamous endothelium. This lining is continuous with the endothelium of the great arteries and veins entering and leaving the heart. It is thicker in the atria than in the ventricles. On the right side of the heart it is frequently interrupted by the entrance of thebesian lacunae

Pathologic Anatomy

Pathologic processes involving the endocardium include infectious and noninfectious

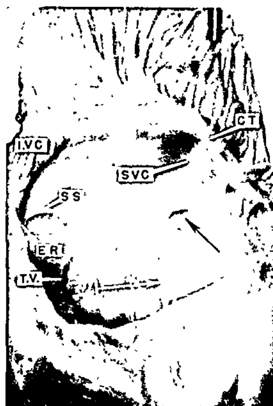


FIG 3 —(B) View of the interatrial septum from the right side, the top of the atrium having been severed along the atrioventricular sulcus and retracted upward Note how the muscular trabeculae of the lateral half of the right atrium radiate peripherally from the crista terminalis (C.T), and how the medial half of the atrium near the septum is smooth, devoid of trabeculations Black arrow indicates the opening of a large vein directly into the atrium (see FIG 9) White arrow lies over the approximate location of the atrioventricular node and bundle of His T V is the thebesian valve, S V C superior vena cava, S S septum secundum of the foramen ovale, and E R the eustachian ridge, which lies between the entrance of the inferior vena cava above (cut open) and the coronary sinus below; I.V C is the opened inferior vena cava

proliferative disorders. Infections are almost always at points of impact by a stream of flowing blood, especially on the cardiac valves The mural endothelium may become infected by bacterial endocarditis when a jet strikes it, e g , the wall opposite the jet of an interventricular septal defect.

Although it was formerly accepted that noninfectious proliferation of the endocardium (endocardial fibroelastosis) was exclusively a disease of infants, evidence now suggests its

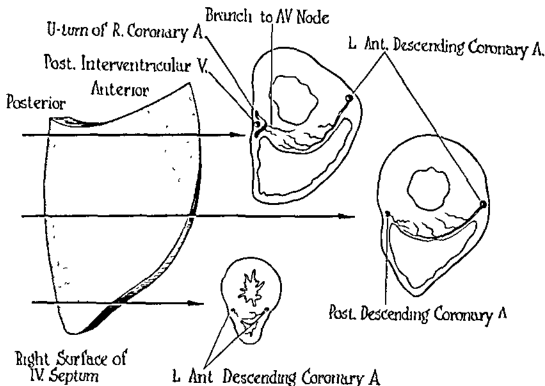
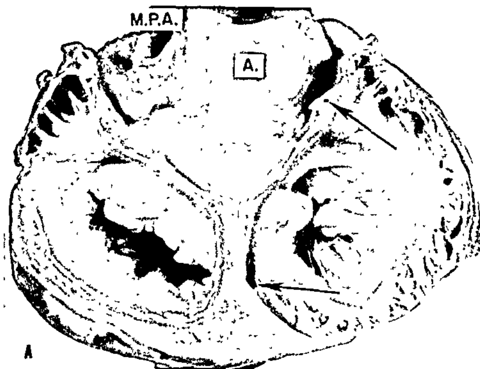


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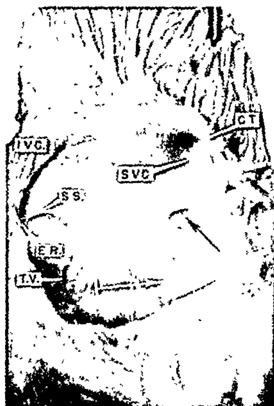


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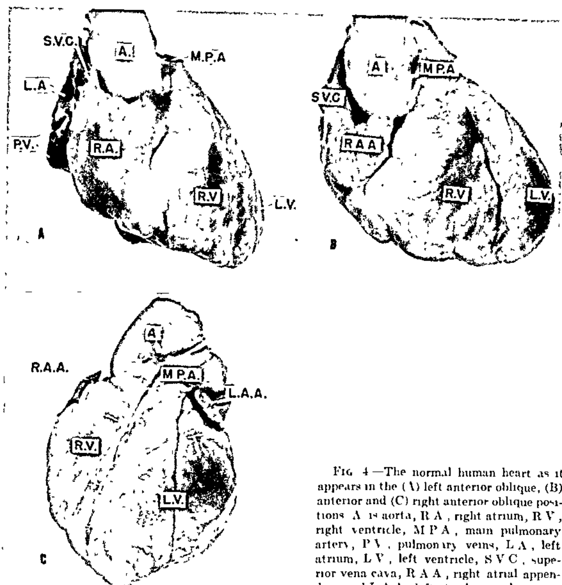


Fig 4—The normal human heart as it appears in the (A) left anterior oblique, (B) anterior and (C) right anterior oblique positions A is aorta, R A, right atrium, R V, right ventricle, M P A, main pulmonary artery, P V, pulmonary veins, L A, left atrium, L V, left ventricle, S V C, superior vena cava, R A A, right atrial appendage and L A A, left atrial appendage

occurrence at any age[23] It is usually manifested by an enlarged heart with a variable but progressively increasing congestive failure in the absence of valvular disease, hypertension and coronary disease Unusual fibrosis of the endocardium of the right side of the heart, especially the valves, occurs in some patients with metastatic malignant carcinoid[16]; the mechanism is unknown but it may be related to the large amount of serotonin reaching the right side of the heart from functioning hepatic metastases

Cardiac Valves

Normal Anatomy

There are four major and two minor valves in the normal adult human heart The four major valves are the two atrioventricular, the aortic and the pulmonary Minor valves are the semilunar venous valves of the inferior vena cava at its entrance into the right atrium (eustachian valve) and of the coronary sinus (thebesian valve), the former is inconstant in the adult

All four major valves must function efficiently to attain normal action Three are tricuspid, the other is the bicuspid mitral valve located between the left atrium and left ventricle Both atrioventricular valves have chordae tendineae attached on their ventricular surface, *the chordae are fixed to the ventricular* myocardium by papillary muscles With contraction of these papillary muscles during systole, the valves are fixed so they do not even-

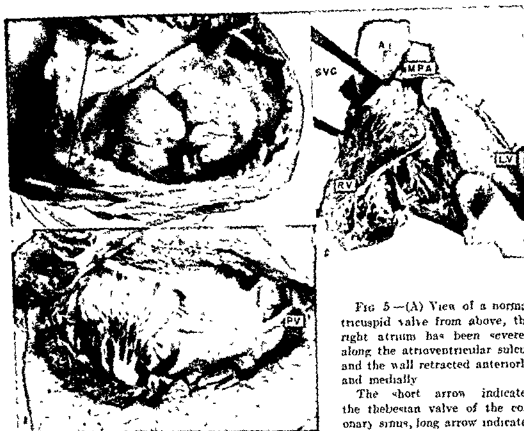


FIG 5—(A) View of a normal tricuspid valve from above, the right atrium has been severed along the atrioventricular sulcus and the wall retracted anteriorly and medially

The short arrow indicates the thebesian valve of the coronary sinus, long arrow indicates the position of the interatrial septum Note the trabeculated lateral half of the atrial wall, and the smooth medial portion (B) The normal tricuspid valve from the same heart as FIGURE 5A, viewed from below An elliptical incision below the anterior atrioventricular sulcus permits retraction of the free right ventricular wall superiorly, the incision is continued in the right upper portion of the photograph across the pulmonary valve (P V) and then parallel to the atrioventricular sulcus to a point near the middle of the visualized tricuspid valve Insertion of the chordae tendineae into the valve leaflets is well shown, as is their origin from the papillary muscles (C) View of human heart opened in the conventional manner, showing one tricuspid valve leaflet tensed open, while the other two lie flat against the endocardium, flow of blood through the valve would be directly toward the viewer The outflow tract of the right ventricle is then in an almost straight vertical direction upward and out the pulmonary valve, the semilunar cusps of which are visualized in the transected pulmonary artery (M P A) A is aorta, S V C, superior vena cava, R V, right ventricle, and L V, left ventricle

trate into the atria The atrioventricular valve leaflets are attached peripherally to the fibrous atrioventricular ring The atrial surface of these valves is smooth, the ventricular part irregular, owing to insertion of chordae The mitral valve leaflets are thicker than those of the tricuspid (FIGS 1, 5 AND 6)

Both the aortic and pulmonic valves are referred to as semilunar valves, since in opening these great vessels, the valve leaflets resemble half-moons Their only attachment is to the wall of the vessel, since chordae tendineae are not present Both valves are constructed similarly, though the aortic is thicker and stronger (FIGS 1 AND 7) At the midpoint of the free edge of each simulunar valve leaflet is a small tendinous tubercle (corpus arantii); and on the wall of the vessel subtended by each leaflet is a gentle recess known in both aorta and pulmonary artery as the sinus of Valsalva These are more prominent in the aorta. In the aorta the anterior sinus faces between the main pulmonary artery and the body of the right atrium and is the site of origin of the right coronary artery, the left posterior sinus faces between the main pulmonary artery and the body of the left atrium and gives rise to the left coronary artery. The remaining

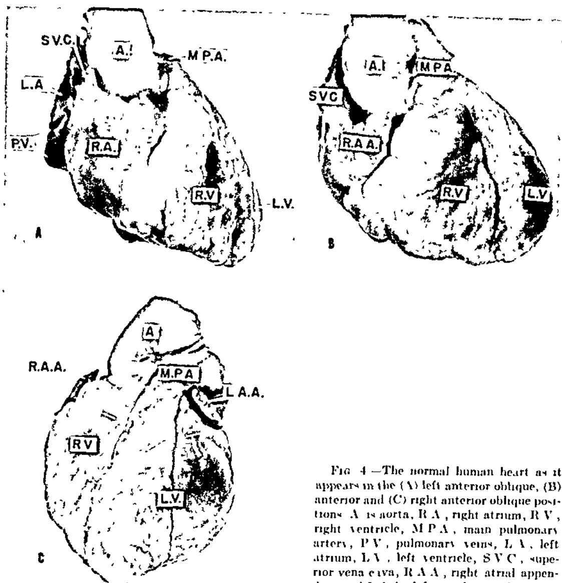


FIG 4 —The normal human heart as it appears in the (A) left anterior oblique, (B) anterior and (C) right anterior oblique positions A is aorta, R A, right atrium, R V, right ventricle, M P A, main pulmonary artery, P V, pulmonary veins, L A, left atrium, L V, left ventricle, S V C, superior vena cava, R A A, right atrial appendage and L A A, left atrial appendage

occurrence at any age [43] It is usually manifested by an enlarged heart with a variable but progressively increasing congestive failure in the absence of valvular disease, hypertension and coronary disease Unusual fibrosis of the endocardium of the right side of the heart, especially the valves, occurs in some patients with metastatic malignant carcinoid[16], the mechanism is unknown but it may be related to the large amount of serotonin reaching the right side of the heart from functioning hepatic metastases

Cardiac Valves

Normal Anatomy

There are four major and two minor valves in the normal adult human heart The four major valves are the two atrioventricular, the aortic and the pulmonary Minor valves are the semilunar venous valves of the inferior vena cava at its entrance into the right atrium (eustachian valve) and of the coronary sinus (thebesian valve), the former is inconstant in the adult.

All four major valves must function efficiently to attain normal action Three are tricuspid, the other is the bicuspid mitral valve located between the left atrium and left ventricle Both atrioventricular valves have chordae tendineae attached on their ventricular surface; the chordae are fixed to the ventricular myocardium by papillary muscles With contraction of these papillary muscles during systole, the valves are fixed so they do not even-

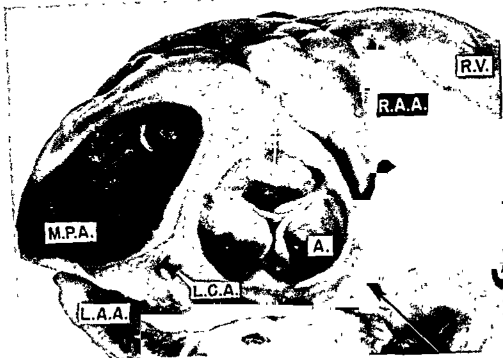


Fig 7 —View looking into the semilunar valves of the main pulmonary artery (M.P A) and aorta (A) The former are thinner and more delicate This specimen is a slice of normal

left atrial appendage, R A A , right atrial appendage, L C A , left coronary artery, and R V., right ventricle

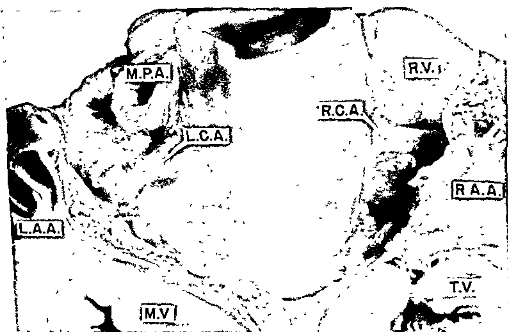


Fig 8 —Normal human heart showing region embraced by the two medial atrial walls at their convergence into the interatrial septum. The noncoronary sinus of the aorta bulges posteriorly into the anterior end of the septum R A A is right atrial appendage, L A A., left atrial appendage, L C A , main left coronary artery, R C A , right coronary artery, M.V , mitral valve, T V , tricuspid valve; M P.A , main pulmonary artery, and R V , right ventricle



Fig 6 —(A) View of a normal human mitral valve from above, the atrial wall severed and retracted anteriorly and medially as in Figure 5A Note that the cut wall is thicker than that of the right atrium and has a smooth endocardial surface (nontrabeculated) Arrow indicates the direction of the interatrial septum (See also Figure 22A, which shows a later stage of the dissection, demonstrating the relationship of the coronary sinus and aorta)



Fig 6 —(B) *Left* The same mitral valve viewed from below The leaflets are thicker than *those of the tricuspid valve The left ventricle has been cut open* in a curved incision to spare the two papillary muscles, the anterior (left arrow) and posterior (right arrow) (C) *Right* Left ventricle of a different human heart which has been opened in a fashion to show both the mitral and aortic valves The two leaflets of the mitral valve are tensed parallel to each other, and it can be seen that both receive chordae tendineae from both papillary muscles The semilunar aortic valves are visible at the base of the opened aorta (A) With the heart closed, flow through the mitral valve is toward the apex and flow out the aortic valve in a parallel but opposite direction M P A is main pulmonary artery, S V C, superior vena cava



Fig 7—Vie[...]ary artery (M P A) and aorta (A) [...]ectate This specimen is a slice of normal human heart w[...]e base and valves, light is visualized through the partially open tricuspid valve on the right Black arrow lies over the interatrial septum and points to the noncoronary sinus of the aorta, white arrow overlies exit of right coronary artery L A A is left atrial appendage, R A A, right atrial appendage, L C A, left coronary artery, and R V, right ventricle

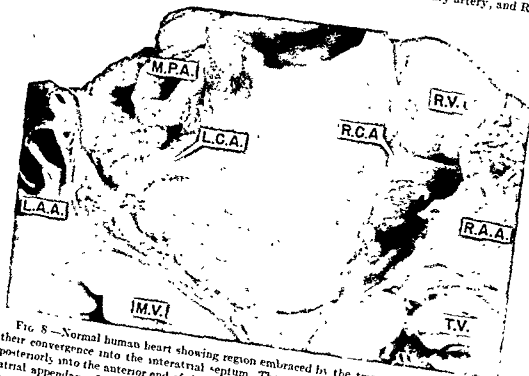


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aortic sinus, the right posterior, is known as the noncoronary sinus (FIG. 8).

Pathologic Anatomy

Normal anatomy of the cardiac valves may be disturbed by congenital or acquired diseases, both of which are discussed in detail in other chapters. These disturbances produce anatomic effects generally in one of two fashions: either by stenosing the orifice of the valve, which impedes forward passage of blood, or in favoring incompetence through distortion, allowing retrograde regurgitation of blood Uncommonly, a valve leaflet may be perforated by trauma or erosive infection, and produce incompetence

Although any of the four major valves may be affected by acquired diseases alone or in combination with other valves, the frequency of involvement corresponds directly to the pressure they are made to bear[13] Thus, the diseased mitral valve is the most common, the aortic second, the tricuspid third and the pulmonic only rarely. It is interesting that despite this relationship, the surface of the valve infected in bacterial endocarditis is usually that opposite to the high pressure side, e g , the atrial surface of the mitral valve and the ventricular surface of the aortic valve This is perhaps related to the traumatizing effects exerted during closure

CONDUCTION CENTERS AND PATHWAYS

Normal Anatomy

The pacemaker of the heart, the *sino-atrial node*, lies at the lateral margin of the junction of the superior vena cava and the right atrium. The node is tapered at the ends and extends posteriorly toward the inferior vena cava; the length is approximately 2 cm Two external landmarks are useful in locating this node: First, a groove (sulcus terminalis) courses between the right atrial appendage and superior vena cava and extends caudad to divide the trabeculated lateral right atrium from the smooth-walled medial half (sinus venarum); inside the atrium there is a ridge (crista terminalis) corresponding to the external groove, (FIG 3B) Second, the ramus ostii cavae superioris (see Coronary Arteries) terminates in the region of the sino-atrial node by encircling the base of the superior vena cava; this circle is particularly easy to visualize in an injection-corrosion specimen of the heart (see Coronary Arteries).

The arterial blood supply to the sino-atrial node is by the artery referred to above, which arises from the left coronary artery in approximately 40 per cent of cases and from the right in 60 per cent Accompanying this arterial circle there is often a venous ring, usually thebesian (FIG. 9)

The *atrioventricular node* is located in the base of the interatrial septum just beneath and slightly anterior to the coronary sinus. The anterior margin continues as a trunk of similar fibers (bundle of His), crossing the junction of the interatrial and interventricular septa and proceeding along the inferior margin of the membranous portion of the interventricular septum At the superior crest of the muscular septum it divides into two separate bundles which cascade down the subendocardium of the two sides of the septum toward the apex of the heart and then ramify distally into the subendocardium of the right and left free ventricular walls (the Purkinje system) On the right side, the bundle consists usually of one or a few branches, whereas the left bundle consists commonly of several branches, some leaving the bundle of His shortly after its origin.

The blood supply to the atrioventricular node and initial portion of the bundle of His is by the ramus septi fibrosi, a branch that penetrates into the junction of the interatrial and interventricular septa from whichever vessel crosses the crux of the heart In 90 per cent of cases this is the right coronary artery The terminal portion of the bundle of His and the proximal portions of the two bundle branches are supplied jointly in varying degrees by branches from the ramus septi fibrosi, an anterior penetrating interatrial artery (Kugel's arteria anastomotica auricularis magna), and the first few penetrating interventricular septal branches of the left anterior descending coronary artery. The remaining portions of the bundle branches are supplied by the interventricular septal branches of the left anterior descending coronary artery almost exclusively,



FIG 9 —Photograph of a vinylite cast of the vessels and chambers of a human heart, the left atrium and ventricle are uncast Three arrows indicate a thebesian vein which filled from the superior vena cava (S V C), this vein accompanied the sinus node artery, the ramus ostii cavae superioris (R O C S) C T indicates the area occupied by the crista terminalis in the intact heart, note the arterial supply to this area C S is the coronary sinus

the penetrating branches of the posterior descending coronary artery being rather short (see Coronary Arteries)

Pathologic Anatomy

Specific disease of these areas has been a neglected subject, in particular, there has been a hiatus in clinical correlation with histopathologic observations A few studies[4, 14] have shown that ischemic changes, such as fibrosis secondary to occlusion of a coronary artery, are common. A number of observers[15, 21] have pointed out that complete heart block may follow posterior myocardial infarction, since the blood supply to the atrioventricular node originates from the artery supplying this region of the ventricle That heart block in such cases is usually transient has been attributed to the efficiency of collateral sources of arterial blood. As may be expected from its multiple supply, vascular insufficiency of the remaining conduction system is seldom an isolated event but is usually associated with damage of surrounding myocardium

Proximity of the atrioventricular node and bundle of His to the fibrous rings of both atrioventricular valves renders them vulnerable to any pathologic process involving these rings (FIG. 3A). Additionally, the bundle of His and initial bundle branches, being adjacent to the aortic valve ring, may become involved by processes originating in that region.

INNERVATION OF THE HEART

Autonomic nerve ganglia are not difficult to demonstrate in histologic sections of the human heart, particularly the atria, but the exact distribution of these nerves is extremely difficult to dissect or otherwise demonstrate. The sympathetic innervation of the heart originates in the upper thoracic spinal cord, and the parasympathetic in the medulla (FIG 10). The sympathetic nerves reach the heart via the superior, middle and inferior cervical ganglia, which produce the superior, middle and inferior cardiac nerves These nerves are joined by branches from both vagus nerves to form the cardiac plexus surrounding the root and arch

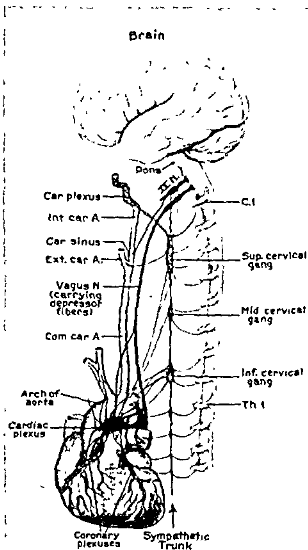


FIG 10 —Schematic representation of innervation of the heart

of the aorta Within the heart are three regions of particular clinical importance to which branches are supplied by the cardiac plexus. The first of these is the sino-atrial node, which is richly innervated The other two regions are the main trunks of the right and left coronary arteries, and the atrioventricular node

In general, the sympathetic fibers of the heart produce cardiac acceleration and the parasympathetic fibers deceleration, probably by influencing the function of the sino-atrial node. The periarterial coronary plexuses may influence spasm and relaxation of these vessels, but evidence to support or refute this in man is inadequate Cardiac reflexes associated with events elsewhere in the body, such as distention of a hollow abdominal viscus, are undoubtedly mediated via the cardiac plexus

CORONARY ARTERIES

Normal Anatomy

There are two major coronary ostia in the human aorta, but in more than half of the hearts in one study[20] there was a distinct but very small third coronary artery (the conus artery) arising separately from the aorta near the right coronary ostium and supplying the region of the pulmonary conus

The *right coronary artery* arises from the anterior sinus of Valsalva and enters the right atrioventricular sulcus pointing slightly to the *right or directly anteriorly It then curves* gently to the right and inferiorly until it reaches the acute margin of the heart, which lies on the diaphragm (FIG 11). At this point it turns in a posterior and medial direction to the crux of the heart In more than 90 per cent of human hearts the right coronary artery crosses the crux of the heart and gives rise to the posterior descending artery[8-10] This latter branch most commonly terminates half way between the crux and the apex or slightly further, but in about one-fourth of cases extends all the way to the apex (FIG 12).

If there is no separate conus artery, the first major branch of the right coronary artery is that supplying the region of the pulmonary conus; it joins with a corresponding branch of the left coronary artery to form a vascular ring exactly at the level of the pulmonic valve and is a major route of collateral arterial flow (FIG 13) *The second major branch of the right* coronary artery is, in approximately 60 per cent of cases, the artery to the sino-atrial node[9] It arises within the first few centimeters of the main artery and passes along the body of the right atrium beneath the atrial appendage and behind the aorta to the anterior interatrial groove, thence, it ascends and encircles the base of the superior vena cava providing nourishing branches to the node (FIG 14). It is classically named the ramus ostii cavae superioris. One other atrial branch of the right coronary artery which is fairly constant is the intermediate atrial branch, which arises near

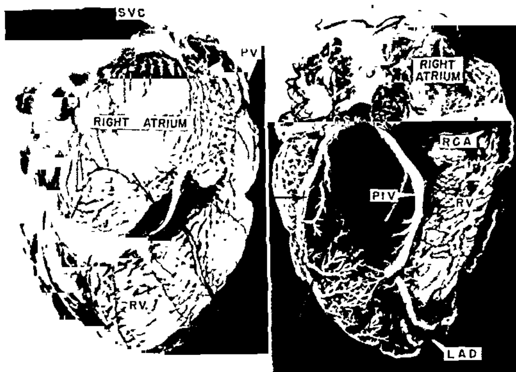
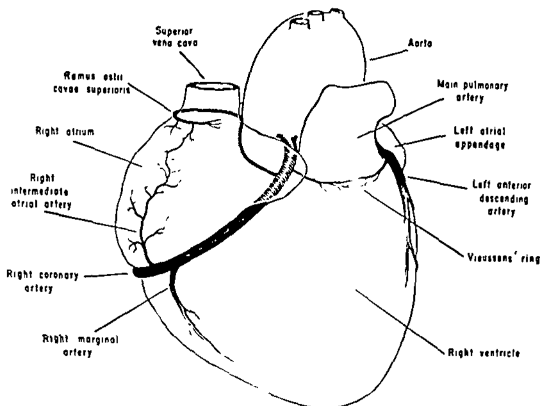


Fig 11 —*Left.* Photograph from the top of the right atrium of a vinylite cast of a human heart Two arrows indicate the right coronary artery. In this view the resemblance of the arteries of the heart to a crown illustrates the origin of their description as "coronary" arteries. R V is right ventricle, P V., pulmonic valves; and S V.C , superior vena cava

Fig 12 —*Right* A cast of a human heart which depicts a common distribution of the right coronary artery (R C A) on the posterior wall of the heart The three arrows outline the area of the posterior left ventricle supplied by the right coronary artery in this heart. Terminal branches of the left anterior descending artery (L A D) supply the posterior apex of the right and left ventricles C S is coronary sinus, P.I.V , posterior interventricular vein; and R.V., right ventricle.



Fig 13 —Three arrows point out the two arteries joining to form Vieussens' ring in this cast of a human heart; the pulmonic valve cusps are not well shown R A A is right atrial appendage. L.A.D., left



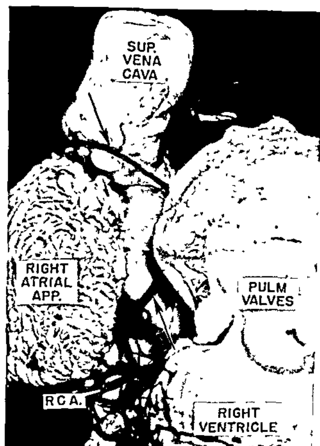


FIG 14.—(A) *Above* Schematic representation of the usual course of the sinus node artery (ramus ostii cavae superioris) when it originates from the right coronary artery (B) *Left* Vinylite cast of a human heart in which the sinus node artery, indicated by two arrows, arose from the right coronary artery (R C A.).

the acute margin of the heart and ascends over the top of the right atrium to terminate near the sino-atrial node, anastomosing with the ramus ostii cavae superioris

Ventricular branches of the right coronary artery in the anterior atrioventricular sulcus leave the artery almost at right angles, characteristically as a sharp loop or curve in a perpendicular plane[10] (Fig 15) They course about two-thirds of the way to the anterior interventricular sulcus, where they meet and anastomose with right ventricular branches of the left anterior descending coronary artery. A large branch usually follows the acute margin of the right ventricle almost to the apex of the heart Posterior right ventricular branches are fewer in number and shorter in length, the area of the right ventricular apex usually is supplied by terminal branches from the left anterior descending coronary artery (Fig 12). The minor divisions of the right ventricular branches are in the same plane as the parent arteries, unlike the smaller branches over the left ventricle (Fig 16)

When the right coronary artery crosses the crux of the heart, it makes a U-turn beneath the posterior interventricular vein, emerging on the ventricular surface again over the posterior surface of the left ventricle (Fig 17). At the apex of this turn the artery to the atrioventricular node (ramus septi fibrosi) is noted. This is the longest of the septal branches of the posterior descending artery, penetrating for a distance of 20 to 40 mm. in the junction of the interatrial and interventricular septa The termination of this branch is at right angles, as are the penetrating branches of the free left ventricular wall. Both this termination and the U-turn beneath the posterior interventricular vein are of embryologic significance.[9]

Originating in the left posterior sinus of Valsalva, the *left coronary artery* only rarely has more than one aortic ostium. Coursing almost directly to the left, the main trunk of the left coronary artery (which varies from 5 to 30 mm. in length) soon divides into the circumflex and anterior descending branches The descending branch curves anteriorly around the base of the main pulmonary artery to enter the anterior interventricular sulcus, there the curve

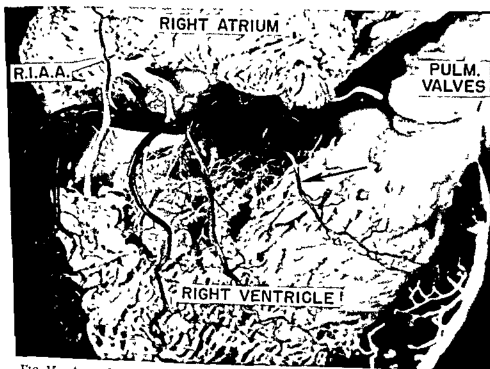
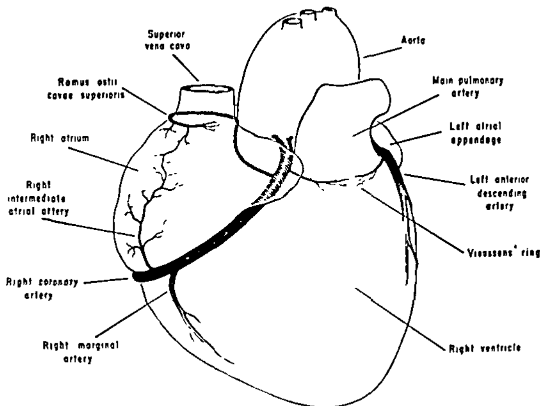


Fig 15—A vinylite cast from a human heart showing the looping origin of the major branches of the right coronary artery, the arrow indicates the first major branch in this heart, the conus artery R I A A is the right intermediate atrial artery



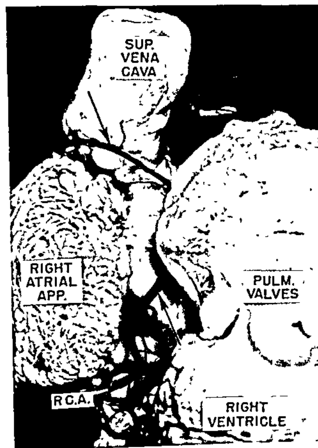


FIG 14—(A) *Above.* Schematic representation of the usual course of the sinus node artery (ramus ostii cavae superioris) when it originates from the right coronary artery. (B) *Left* Vinylite cast of a human heart in which the sinus node artery, indicated by two arrows, arose from the right coronary artery (R C A.).

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Ventricular branches of the right coronary artery in the anterior atrioventricular sulcus leave the artery almost at right angles, characteristically as a sharp loop or curve in a perpendicular plane[19] (Fig. 15). They course about two-thirds of the way to the anterior interventricular sulcus, where they meet and anastomose with right ventricular branches of the left anterior descending coronary artery. A large branch usually follows the acute margin of the right ventricle almost to the apex of the heart. Posterior right ventricular branches are fewer in number and shorter in length; the area of the right ventricular apex usually is supplied by terminal branches from the left anterior descending coronary artery (Fig. 12). The minor divisions of the right ventricular branches are in the same plane as the parent arteries, unlike the smaller branches over the left ventricle (Fig. 16).

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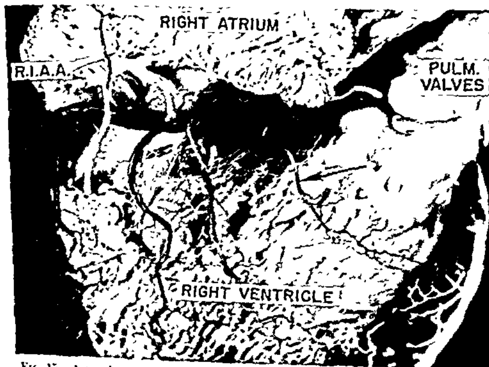
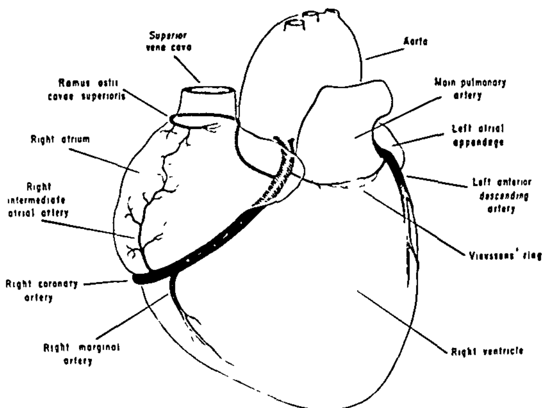


Fig. 15.—A vinylite cast from a human heart showing the looping origin of the major branches of the right coronary artery; the arrow indicates the first major branch in this heart, the conus artery. R.I.A.A. is the right intermediate atrial artery.



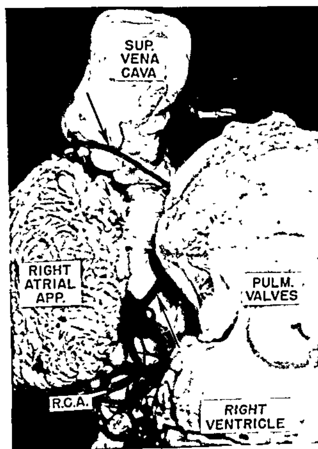
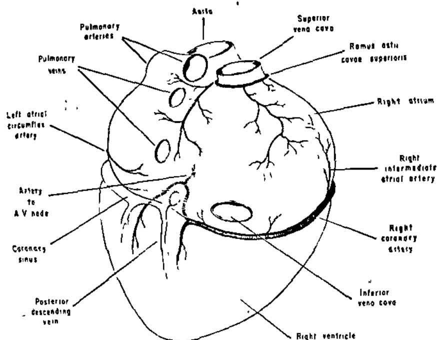


FIG 14 —(A) *Above* Schematic representation of the usual course of the sinus node artery (ramus ostii cavae superioris) when it originates from the right coronary artery (B) *Left* Vinylite cast of a human heart in which the sinus *node artery*, indicated by two arrows, arose from the right coronary artery (R C.A).



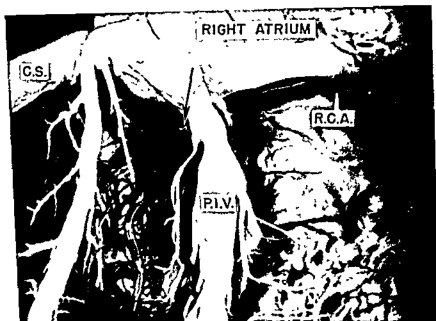


FIG 17 —(A) *Above* Drawing of the right coronary artery at the crux of the heart, showing the U-turn around the posterior interventricular vein and beneath the coronary sinus, the artery to the A V. node (ramus septi fibrosi) arises from the apex of the U and terminates in right angle branches, just as do the terminal branches of the free left ventricular wall (Courtesy of James and Burch [9]) (B) B... [illegible] ...e heart along the posterior interventricular [illegible] artery; the arrow indicates the direction of tl[illegible] ...ht coronary artery (R C A) after the U-turn course parallel to the posterior interventricular vein (P.I V) as the posterior descending artery C S. is coronary sinus Left atrium and left ventricle are uncast

cardium, penetrating the septal myocardium terminally (FIG 2) These branches are long, measuring 40 to 80 mm Only the posterior third of the interventricular septum receives branches from the right coronary artery, but these branches anastomose with those from the anterior descending artery.

After curving around the apex cordis, the

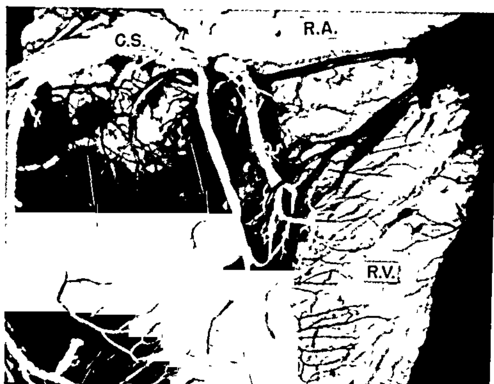


FIG 16—Differential branching over the two ventricles is shown in this cast The view is of the posterior wall in the region of the crux Terminal branches of both the right coronary artery (*right arrows*) and left marginal artery (*left arrows*) turn perpendicularly to the surface of the heart to penetrate the thick left ventricular myocardium Note by contrast how the right ventricular branches of the same right coronary artery terminate in a plane parallel to the parent artery C S is coronary sinus, R A, right atrium, and R V, right ventricle As usual, the left atrium and left ventricle were intentionally uncast

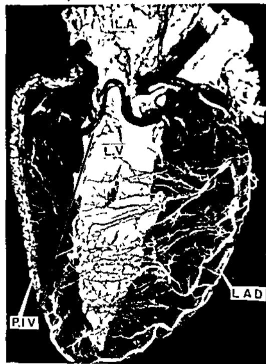
is slightly reversed so that if viewed from the front there appears a reverse S-curve (FIG. 18) In approximately 80 per cent of cases the artery extends around the ventricular apex to ascend a variable distance in the posterior interventricular sulcus to meet the terminal branches of the posterior descending artery (in more than 90 per cent of cases the right coronary artery).

From its origin, the left circumflex coronary artery circles to the left in the atrioventricular sulcus. In more than 80 per cent of hearts it terminates along the margo obtusus or slightly beyond, as the left marginal artery, when it does cross the crux of the heart, which is rare in man (but usual in dogs), it provides the posterior descending artery.

A variable number of large branches arise from both rami of the left coronary artery to supply the wall of the left ventricle Unlike the branches over the right ventricle, these usually terminate by turning perpendicularly to the surface of the heart and penetrating to the subendocardium This same type of termination is true of arteries on the surface of the left ventricle whether they arise from the left or right coronary artery (FIG 16).

In addition to branches to the left ventricular wall, the left anterior descending coronary artery also supplies some branches to the right ventricle and most of the blood supply to the interventricular septum [11] The right ventricular branches are most often in two groups: The first completes the arterial ring at the level of the pulmonic valve by joining corresponding vessels from the right coronary artery; the second group is a variable number of small straight branches near the midpoint of the anterior interventricular sulcus

Branches to the interventricular septum course posteriorly and slightly inferiorly, arising at irregular intervals from the anterior descending artery (FIG 19). Most of their course, at least initially, is in the right septal subendo-



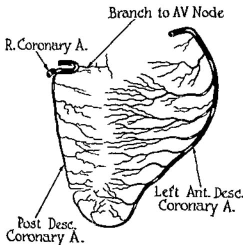


FIG 19—(A) *Above* Schematic drawing of the arterial supply to the human interventricular septum (Courtesy of James and Burch [11]) (B) *Left* Vinylite cast of a human heart viewed from the right, with the free wall branches of the right coronary artery cut away to reveal the arteries of the interventricular septum The long arrow divides the anterior portion of the septum, supplied by branches of the left anterior descending coronary artery (L A D), from the posterior portion, supplied by the posterior descending branch of the right coronary The latter courses parallel to the posterior interventricular vein (P I V) and comprises the dark branches seen between the vein and the arrow The right coronary artery is the dark undulating vessel out of focus at the top L A and L V. are left atrium and left ventricle, the right chambers being uncast in this specimen Note the preponderance of the arterial supply to the septum by the left coronary artery

varying point on the left circumflex artery and thence runs parallel to it but at a slightly higher level, being located in the base of the left atrium (FIG. 21). It has been designated the left atrial circumflex artery[9] and is important as a major source of blood supply to the left atrium. The artery sometimes terminates by recrossing the atrioventricular sulcus posteriorly to supply the posterior left ventricular wall

As implied in the preceding descriptions, the right and left coronary arteries and their branches anastomose with each other throughout the normal heart. For many years it has been held that normally occurring anastomoses do not exceed 40 micra in diameter, and conversely that larger anastomoses occur only with certain diseases that render the myocardium anoxic, such as coronary atherosclerosis or anemia[23] A number of recent studies[2, 12, 24] suggest that this is a conservative concept, and that anastomoses as large as 1,000 micra (1 mm.) may exist in normal hearts. Whether these anastomoses function as collateral sources of blood supply remains a question, principally for lack of a satisfactory means to demonstrate such function.

Areas in the normal heart in which anastomoses are easily demonstrable are along either side of the two interventricular sulci, in the interventricular septum, around the apex cordis, at the level of the pulmonary valve ring (the ring of Vieussens or of Cruvelhier) and across the top of either atrium between small arteries. There are also connecting vessels

Pathologic Anatomy

Atherosclerosis is the most common disease of the coronary arteries. It is present in in-

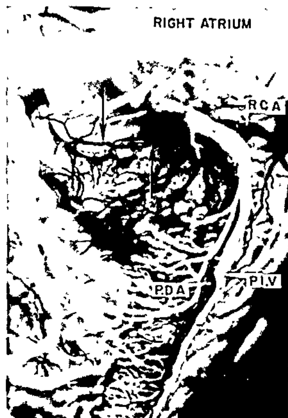


FIG 17.—(C) Arrows indicate the artery to the A V node (ramus septi fibrosi) Photograph was made through branches of the left coronary artery which are intentionally out of focus in the foreground The horizontal cleft visible just below the A V node artery is the location of the fibrous atrioventricular ring of the tricuspid valve R C A is right coronary artery, P I V posterior interventricular vein, and P D A, posterior descending artery Left atrium and left ventricle are uncast

left anterior descending coronary artery terminates in the lower half of the posterior interventricular sulcus. It sends branches to the posterior apical portions of both the left and right ventricles

The left circumflex coronary artery has the principal mission of supplying the anterior and lateral walls of the left ventricle In 40 per cent of hearts, this artery (or the main left coronary artery) also supplies the sino-atrial node, in less than 10 per cent, it crosses the crux and supplies the atrioventricular node When the sino-atrial nodal artery arises from the left side, it is usually from within 1 cm of the bifurcation of the left coronary artery, proximally or distally, in the latter case arising from the left circumflex artery From this origin, it passes medially along the body of the left atrium, beneath the atrial appendage and behind the aorta, to the anterior interatrial septal groove; thence it terminates, resembling its right counterpart, by ascending to the base of the superior vena cava and encircling to supply the sino-atrial node (FIG 20). Although there is usually communication between atrial branches of the right and left coronary in this region, the principal supply to the node is almost always from one side or the other and not bilateral

When the left circumflex coronary artery crosses the crux of the heart, as with the right counterpart, it also makes a U-turn beneath the posterior interventricular vein The artery to the atrioventricular node in these cases also arises from the U-turn and penetrates anteriorly in the junction of the atrial and ventricular septa

The only other common atrial branch of the left coronary artery is one that arises at a

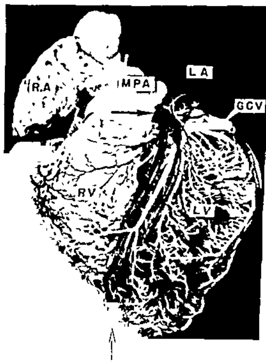


FIG. 18.—Vinylite cast of a human heart (*front view*) Two arrows indicate the visible upper and lower ends of the left anterior descending coronary artery, which typically pursues a gentle reverse S-curve R V is right ventricle, R A, right atrium, M P A, *main pulmonary artery*, and G.C V., great cardiac vein. L A and L V indicate the positions of the uncast left atrium and left ventricle



FIG 21.—Cast of human heart showing the left atrial circumflex coronary artery, indicated by two arrows L Circ is the left circumflex artery (ventricular), shown terminating as the left marginal artery; L A D., the left anterior descending coronary artery, A, aorta, M P A, main pulmonary artery; R O C S, ramus ostii cavae superioris (sinus node artery); and G C V, great cardiac vein Left atrium and left ventricle are uncast

creasing degrees from birth and has a predilection for males, although this is less striking after the age of 50 years [1, 3, 17] The symptoms depend on two anatomic factors: first, the extent of compromise of the lumen of the artery and second, the location of this luminal encroachment. Secondarily, manifestations depend on the extent and ready availability of blood from collateral sources Gradual occlusion of a coronary artery by an atheroma is usually accompanied by efficient concomitant development of collateral blood supply. This development takes place from neighboring arteries in all directions and is more efficient in the proximal course of the main coronary trunks, an important compensation, for this is also the region of most extensive and usual involvement by atherosclerosis. The inefficiency of collaterals in the terminal coronary tree is demonstrated by the fact that the two most common locations of myocardial infarction are at the anterior left ventricular apex and at the crux of the heart, representing the termination of the left anterior descending and right coronary arteries, respectively.

When coronary occlusion is proximal to the arteries supplying the sino-atrial node or atrioventricular node, disturbances in the function of these nodes, such as atrial arrhythmias or atrioventricular conduction disturbances, are commonly seen. Since the blood supply of the atrioventricular node is from the artery crossing the crux of the heart (in more than 90 per cent of cases the right coronary artery), atrioventricular block is virtually always a manifestation of posterior myocardial infarction and occlusion of the right coronary artery.

Another disease that alters coronary anatomy is syphilis, with its unique feature of stenosing the coronary ostia. Aneurysms of the coronary arteries may follow mural weakening by any inflammation (including septic "mycotic" emboli), or may be the result of congenital weakness. Their rupture, externally, is fatal, whereas rupture back into a cardiac chamber becomes symptomatic, owing to the development of a fistula If the rupture occurs into one of the right chambers of the heart, an arteriovenous fistula results.

VEINS OF THE HEART

Normal Anatomy

There are three separate systems of veins in the human heart. The largest system, which drains most of the left ventricular venous blood, terminates in the coronary sinus and empties into the right atrium (FIG. 22). The second system of large veins drains the right ventricular venous blood and empties into the right atrium separately from the coronary sinus (FIG. 23) The small veins (thebesians) are important only on the right side of the heart, where they drain a varying portion of the myocardial venous blood directly into the right atrium and right ventricle (FIG. 9).

The anterior interventricular vein ascends from the apex of the heart to the region of the

Superior vena cava
Aorta
Ramus ostii cavae superioris
Right coronary artery
Right atrium
Pulmonary veins
Main pulmonary artery
Right ventricle
Arteria anastomotica auricularis magna
Left anterior descending artery
Left atrium
Left intermediate atrial artery
Left atrial circumflex artery
Left marginal artery
Left circumflex artery
Left ventricle

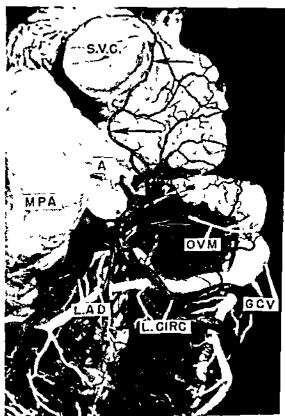


FIG 20—(A) *Above* Drawing of the sinus node artery (ramus ostii cavae superioris) when it arises *from the left coronary artery* *Kugel's artery* (arteria anastomotica auricularis magna), which courses in the base of the interatrial septum, is shown (Courtesy *of James and Burch*[9]) (B) *Left* Vinylite *cast of a* human heart with the sinus node artery, indicated by three arrows, arising from the left circumflex coronary artery (L Circ) A is aorta, M P A , main pulmona
coronary
oblique
cava

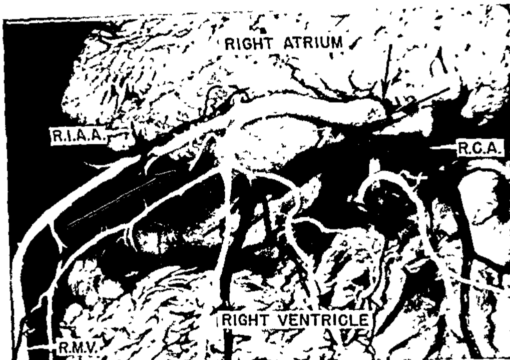


FIG 23 —Vinylite cast (human heart) of the anterior cardiac veins which drain the right ventricle This particular group drains in the direction of the large arrow on the left to empty into the right atrium at the point indicated by the two arrows on the right R.M.V is the right marginal vein, R I A A , right intermediate atrial artery, and R C A , right coronary artery. Unlike the other anterior cardiac veins, the one furthest to the right goes through several loops and passes beneath the right coronary artery before joining the large subintimal vein of the right atrium just prior to its emptying into the right atrium Also visible are major branches of the right coronary artery descending into the region of the tricuspid valve.

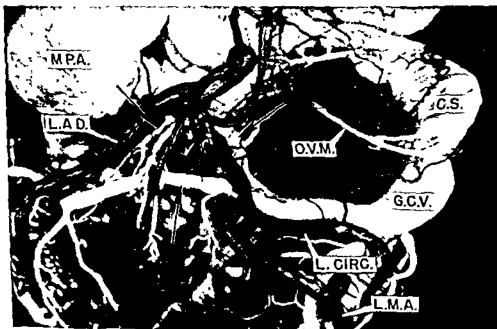


FIG 24 —Vinylite case (human heart) showing the great cardiac vein divided into a plexus of veins near the *origin* of the left circumflex coronary artery (L Circ), indicated by three arrows In *some hearts*, the plexus consists of a large number of very small vessels M P A is main pulmonary artery , L A D , left anterior descending coronary artery, O V M , oblique vein of Marshall, L M A., left *marginal* artery, G C V , great cardiac vein, and C S , coronary sinus Left atrium and left ventricle are uncast

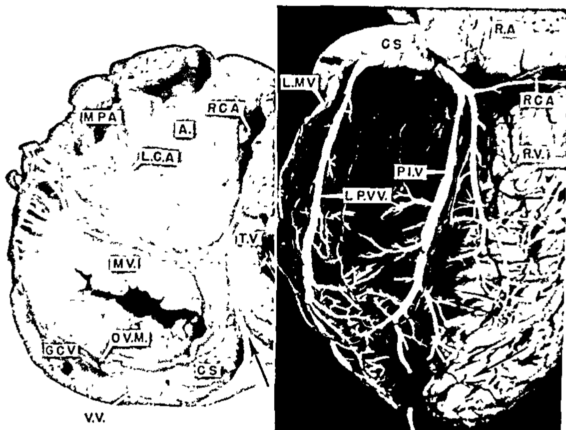


FIG 22.—(A) Normal human heart showing the coronary sinus (C S) and great cardiac vein (G C V), these are virtually a continuous vessel, the point of division being the filmy valve of Vieussens (V V) Just beyond the valve is the oblique vein of Marshall (O V M) which ascends the posterior left atrial wall and here has been cut, it is the remnant of the fetal left superior vena cava M P A is the main pulmonary artery, M V, mitral valve, T V., tricuspid valve, L C A, left coronary artery, R C A, right coronary artery, and A, aorta Arrow indicates the thebesian valve at the exit of the coronary sinus into the right atrium (B) View of the coronary sinus (C S) and its major posterior tributaries L M V is the left marginal vein, L P V V, left posterior ventricular vein, and P I V, posterior interventricular vein The small cardiac vein, an inconstant tributary of the posterior interventricular vein, is shown running directly across the right coronary artery (R C A) R A and R V are right atrium and right ventricle, the left chambers are uncast

bifurcation of the left coronary artery, where it may continue laterally by curving into the atrioventricular sulcus as a single trunk, but sometimes divides into a plexus of veins at this point, reforming a single trunk as it parallels the left circumflex coronary artery (FIG. 24). At this point it is called the great cardiac vein, continuing on to form the coronary sinus, which empties into the right atrium through the posterior inferior corner of the interatrial septum; this exit is partially closed by a single semilunar valve The point at which the great cardiac vein becomes the coronary sinus is marked by the origin of the oblique vein of Marshall (FIGS. 22A AND 25), a remnant of the left superior vena cava of the fetus.

Major tributaries of the coronary sinus include *the left marginal vein of the heart*, ascending along the obtuse margin, and the posterior interventricular vein The venous blood of the free left ventricular wall is drained by the anterior and posterior interventricular veins and the left marginal vein; other veins, which vary in size, may occur between these and usually parallel major arteries Venous blood from the interventricular septum drains into the anterior and posterior interventricular veins. Except for the oblique vein of Marshall the atrial veins are relatively inconstant, nu-

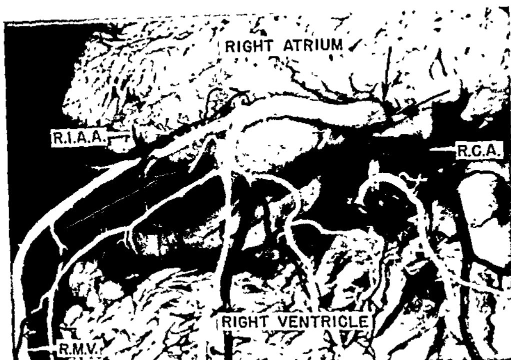


FIG 23 —Vinylite cast (human heart) of the anterior cardiac veins which drain the right ventricle This particular group drains in the direction of the large arrow on the left to empty into the right atrium at the point indicated by the two arrows on the right R M V is the right marginal vein, R.I A A , right intermediate atrial artery, and R C A , right coronary artery. Unlike the other anterior cardiac veins, the one furthest to the right goes through several loops and passes beneath the right coronary artery before joining the large subintimal vein of the right atrium just prior to its emptying into the right atrium Also visible are major branches of the right coronary artery descending into the region of the tricuspid valve

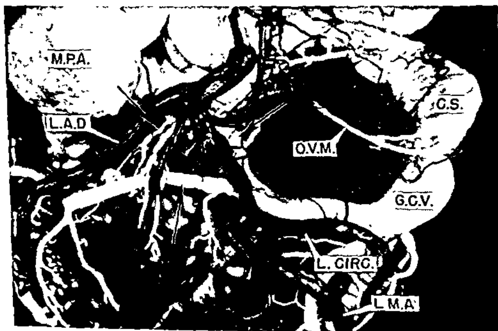


FIG 24 —Vinylite case (human heart) showing the great cardiac vein divided into a plexus of veins near the origin of the left circumflex coronary artery (L. Circ), indicated by three arrows. In some hearts, the plexus consists of a large number of very small vessels M P A is main pulmonary artery, L A D , left anterior descending coronary artery, O V M , oblique vein of Marshall, L M A , left marginal artery, G C V , great cardiac vein, and C S , coronary sinus Left atrium and left ventricle are uncast

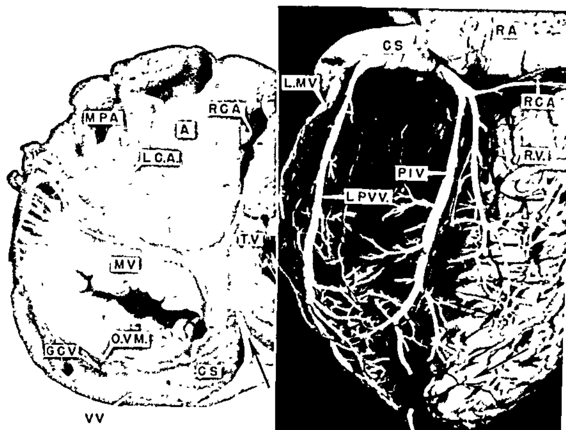


FIG. 22.—(A) Normal human heart showing the coronary sinus (C.S.) and great cardiac vein (G.C.V.); these are virtually a continuous vessel, the point of division being the filmy valve of Vieussens (V.V.). Just beyond the valve is the oblique vein of Marshall (O.V.M.) which ascends the posterior left atrial wall and here has been cut; it is the remnant of the fetal left superior vena cava. M.P.A. is the main pulmonary artery, M.V., mitral valve, T.V., tricuspid valve, L.C.A., left coronary artery, R.C.A., right coronary artery, and A., aorta. Arrow indicates the thebesian valve at the exit of the coronary sinus into the right atrium. (B) View of the coronary sinus (C.S.) and its major posterior tributaries. L.M.V. is the left marginal vein, L.P.V.V., left posterior ventricular vein, and P.I.V., posterior interventricular vein. The small cardiac vein, an inconstant tributary of the posterior interventricular vein, is shown running directly across the right coronary artery (R.C.A.). R.A. and R.V. are right atrium and right ventricle; the left chambers are uncast.

bifurcation of the left coronary artery, where it may continue laterally by curving into the atrioventricular sulcus as a single trunk, but sometimes divides into a plexus of veins at this point, reforming a single trunk as it parallels the left circumflex coronary artery (FIG. 24). At this point it is called the great cardiac vein, continuing on to form the coronary sinus, which empties into the right atrium through the posterior inferior corner of the interatrial septum; this exit is partially closed by a single semilunar valve. The point at which the great cardiac vein becomes the coronary sinus is marked by the origin of the oblique vein of Marshall (FIGS. 22A AND 25), a remnant of the left superior vena cava of the fetus.

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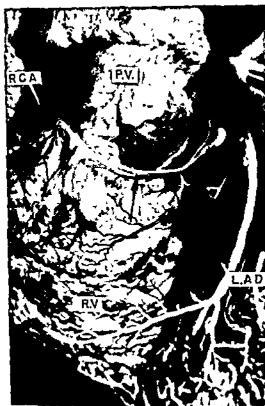


FIG 26—Vinylite cast (human heart) showing a venous ring of Vieussens, indicated by three arrows A small accompanying artery is seen below the vein in the right half. This ring is rather constantly at the level of the pulmonary valves (P V). R.C A is right coronary artery, R V., right ventricle, L A D , left anterior descending coronary artery The venous ring connects the left anterior interventricular vein, seen accompanying the left anterior descending artery, and one of the right anterior cardiac veins, this ring is thus one ready means of communication between right and left ventricular venous blood

tension, reflected in the right ventricle, may impair normal drainage by both the thebesian and anterior cardiac veins. This was postulated to decrease the efficiency of blood supply by the right coronary artery to the right ventricle, favoring the development of right heart failure[18]

Lymphatic System of the Heart

Normal Anatomy

What meager knowledge of this subject is available has been lucidly reviewed in an atlas on the lymphatic system by Rouviere[19] There is disagreement as to whether lymphatic vessels exist within the myocardium or not, strong evidence being available for either argument. There is slightly better evidence that the endocardium has lymphatic vessels, though the course of drainage is not clear.

There is little dispute regarding the epicardial lymphatic system, which is simpler to demonstrate and consequently more thoroughly studied (FIG. 27). Lymph from the surface of the left ventricle is collected by two trunks near the anterior interventricular sulcus and a third from the atrioventricular sulcus. These three trunks unite near the bifurcation of the left coronary artery and drain as a single vessel up along the main pulmonary artery to a node at the tracheal bifurcation

The lymphatic vessels of the right ventricle all drain into a single trunk which courses through the atrioventricular sulcus from posterior to anterior, terminating as a trunk as-



FIG 27—Human heart fixed in formalin but unstained or otherwise altered showing in faint outline the epicardial lymphatic vessels of the left ventricle Two trunks originate at points indicated by the two lowest arrows, they converge at the right upper arrow and their common trunk unites with a vessel accompanying the left anterior descending coronary artery (L A D) at the left upper arrow These then divide into two main channels which drain up the main pulmonary artery (M P A) and aorta (A), respectively. L A A is left atrial appendage; L V , left ventricle.

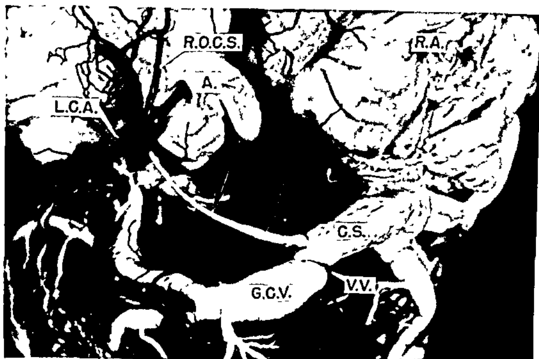


FIG 25 —Vinylite cast (human heart) showing the oblique vein of Marshall, indicated by two arrows This is the remnant of the fetal left superior vena cava and persists usually as a small posterior left atrial vein, but sometimes only as a fibrous cord Left atrium and left ventricle are uncast L C A is left coronary artery, R O C S, ramus ostii cavae superioris (sinus node artery), A, aorta, G C V, great cardiac vein, V V, valve of Vieussens, dividing the great cardiac vein and coronary sinus (C S), and R A, right atrium

merous small ones being present in varying locations.

On the anterior surface of the right ventricle major veins ascend to cross the atrioventricular sulcus and right coronary artery at right angles (FIG. 23). These veins vary in number, most commonly being 3 or 4, including one large vein along the acute margin of the heart. They empty into the right atrium in one of two fashions, either separately along its anterior wall, or by draining into a collecting vein in the base of the anterior right atrium. This latter vein courses parallel to and above the atrioventricular sulcus from the anterior atrium around the acute margin to empty into the posterior atrium near the entrance of the inferior vena cava, on the opposite side from the coronary sinus; sometimes it drains in the opposite direction, entering the right atrium anteriorly (FIG 23)

The large venous systems as described above communicate abundantly with each other, especially near the interventricular sulci, in the interventricular septum and at the apex. They also communicate freely between their own system of branches At the level of the pulmonic valve there is a venous ring which corresponds to the arterial ring (FIG 26).

The small (thebesian) veins of the heart play a major role in venous drainage of the right atrium and ventricle Facts regarding their anatomic and physiologic significance are difficult to obtain because they are small, numerous, variable and generally separated from each other. In the right atrium they are numerous in the right side of the septum, in the appendage and the lateral wall, but infrequent in the sinus venarum They are numerous throughout the right ventricular free wall as well as on the right side of the ventricular septum.

Pathologic Anatomy

Diseases of the cardiac veins are rarely of clinical significance; phlebitis of the coronary sinus may occur [6] Post-traumatic and congenital fistulae between a vein and neighboring coronary artery have been described.

Perhaps of more clinical significance is the experimental evidence that pulmonary hyper-

The Normal and Pathologic Physiology of the Myocardium

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INTRODUCTION

THE myocardium is a compact syncytium of contractile units Its unique function is the rhythmic propulsion of blood into the systemic and pulmonary circulations

In health, the myocardium has the striking capability of adapting its performance to the existing demand and of efficiently integrating its work with the function of the peripheral vessels so that a proper flow of blood is assured to all of the tissues.

This sensitive response to all manners of stress may be altered considerably by various disease states If, in the course of events, myocardial function is disturbed to a point at which its primary physiologic obligation of maintaining an output equal to metabolic requirements is forfeited, death of the organism finally results. It is quite apparent, therefore, that the mechanisms which initiate, maintain and regulate contraction of the cardiac muscles are matters of exceptional importance.

The format for the present inquiry into the matter includes a discussion of (1) the initiation and propagation of the cardiac impulse, (2) the cardiac contraction, (3) the regulation of cardiac output and (4) myocardial metabolism.

THE INITIATION AND PROPAGATION OF THE CARDIAC IMPULSE

Structural Components

The myocardium, sinoatrial and atrioventricular nodes and the conduction tissue are the essential specialized tissues for the initiation and conduction of the cardiac impulse.[7]

The walls of the heart consist of sheets of anastomosing myocardial fibers which form a syncytium throughout the entire muscle mass. Although normally there is not any muscular connection between the atria and the ventricles, an abundant anastomosis links each of these structures with its respective septum.

The individual myocardial fibers contain numerous cross striated myofibrils which, in turn, consist of periodic, beaded myofilaments, the fundamental contractile unit of the heart.[5]

The sinoatrial node is located at the right anterior junction of the superior vena cava and the right atrium. It is about 25 mm. in length and may be divided into a head, body and tail. Both the head and tail are connected intimately with the atrial fibers by a transitional type of muscle cell thereby enhancing the spread of the impulse to the atria. It is in the sino-atrial node that the heart beat originates. The resultant rhythm is known as sinus rhythm.

The atrioventricular node is formed at the junction of the right atrium with the ventricles near the coronary sinus and the adjacent atrial septum. It is about 5 mm. in length and 2 to 3 mm in diameter.[8]

The uppermost portion of the node which is joined with the atrial muscle fibers by a transitional type of cell is known as the coronary node The remainder of the atrioventricular node may be subdivided into an upper portion which rests in the interatrial septum, a middle section which is placed in the connective tissue of the atrioventricular junction and a lower node which lies in the interventricular septum adjacent to the membranous area The atrioventricular node is a reserve or secondary pacemaker. The rhythms arising from it are known as nodal and are further classified as coronary, upper, middle or lower depending on the exact section in which they originate.

The common atrioventricular bundle is a continuation of the atrioventricular node and lies immediately behind the membranous por-

cending on the anterior surface of the aorta. This trunk empties into a lymph node of the anterior mediastinal group located in front of the origin of the left common carotid artery.

The lymphatic vessels of the atrial epicardium are less numerous than those of the ventricular segment, and the course is more variable. Some empty into the collecting trunks of the ventricular lymphatic system, but others drain in all directions, connections having been demonstrated with lymph nodes of the trachea, hila of the lungs and diaphragm

Pathologic Anatomy

Information regarding this subject is virtually nonexistent. The lymphatic vessels probably play an important role in metastasis of tumors to the heart, and may contribute in some fashion to altered metabolism associated with cardiac failure.

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tivated 0.08 to 0.12 seconds after the initiation of the impulse.[14]

It is currently believed that a specialized conduction path does not exist between the sino-atrial and the atrioventricular nodes but that the activation process arrives at the latter area in the course of its natural spread through the atrial muscle Here, the rate of transmission is relatively slow. The time required for conduction is estimated at approximately 0 05 second by which time the atria have completed their systole.

The excitation passes from the atrioventricular node to the atrioventricular bundle where the speed of transmission increases rapidly to 4,000 mm. per second and is maintained at the rate throughout the entire Purkinje system.[1]

Normally, the initial part of the ventricles to be stimulated is the left lower aspect adjacent to the septum two-thirds of the way from the base to the apex. The excitation then spreads out radially to the rest of the septum but arrives at the basal portion last The process continues from the septum to the papillary muscles and then spreads over the lateral walls of the ventricles as a circular front which activates the endocardial tissue prior to the epicardial surface. All parts of the ventricles are activated in 0 08 to 0 10 second and the entire surface of the two ventricles within 0.04 second of each other

Under normal conditions, every section of the heart is activated within 0.25 second after the impulse is propagated from the sino-atrial node. The mechanism of conduction assuring this remarkable response is considered to be dependent on the sequential depolarization of the cellular membrane Following depolarization, a period elapses during which the membrane cannot respond to an additional stimulus. This is known as the absolute refractory period. It is succeeded by a relative refractory period during which a response can be evoked only by a particularly strong stimulus In the interval occupied by the absolute and relative refractory periods, recovery of the membrane potential is taking place The speed of this process is a reflection of local metabolic activity and is not causally related to the velocity with which the impulse is propagated initially.

The important variations of conductivity which are held responsible for the failure of impulse propagation in the heart include delayed conduction, concealed conduction, unidirectional conduction and complete failure of conduction.

A delay in impulse transmission may develop when alterations in local sources of energy produce a uniformly depressed excitability in a stretch of tissue. It may also result when a gradient of excitability exists between two tissue areas and is of such a magnitude as to arrest but not halt the stimulus.

When an impulse is halted within the depressed tissue and not at its boundary with a normal area, concealed conduction is said to exist. The block in the depressed stretch develops because of the resistance offered by a single unit with an unusually high threshold of excitability and cannot be differentiated from stoppage at the boundary

An impulse initiated in normal tissue is more apt to traverse an intervening depressed area than one propagated in abnormal tissue. Since a stimulus may be blocked out depending on the point and circumstances of its origin, conduction in effect may be unidirectional.

A complete failure of impulse transition occurs under normal conditions during the absolute refractory period when the membrane will not respond to any form of stimulus. It may also develop under abnormal circumstances when the refractory period is prolonged beyond the usual interval because of local metabolic disturbances within the cell.

Excitability. Excitability is that property through which muscle responds when it is stimulated Under ordinary circumstances, when tissue has greater excitability, it requires a lesser stimulus for a fixed response, or, otherwise expressed, offers a greater response to a fixed stimulus. However, if quiescent cardiac muscle is excited with a series of single stimuli which are progressively increased in strength and properly spaced, it will not respond until a critical intensity is reached A further increase in the excitation will not augment the strength of this contraction. Thus, the ventricle responds in a maximum fashion or not at all. The "all or none" law does not imply that the response

proximately 10 mm. in length. At its lower end, the bundle splits into two sections. The right branch spreads out beneath the endocardial surface of the interventricular septum almost as a direct continuation of the common bundle. The left branch crosses over to the left side and branches extensively within the subendocardium. The terminal fibers of both branches anastomose directly with the muscle fibers of the ventricle at all depths of the myocardium both in the outer walls and in the septum.[4, 5]

The blood supply to the sino-atrial and atrioventricular nodes, to the common bundle, to the main stem of the right branch and to a portion of the main stem of the left is derived from special divisions of the right coronary artery. The left coronary vessel supplies the major portion of the main stem of the left bundle and its anterior branchings.

Vagus and sympathetic nerve fibers are found in all the component parts of the specialized tissues for the initiation and conduction of the cardiac impulse.

Physiologic Properties

The properties of rhythmicity, conductivity and excitability are concerned with the initiation and propagation of the cardiac impulse.[7]

Rhythmicity. In the mammal, the cardiac impulse is repeatedly initiated in the sino-atrial node.[10] This property of rhythmicity resides in and is peculiar to nodal and not neurogenic tissue.

The mechanism responsible for the rhythmic discharge of impulses from the sino-atrial node has not been defined. However, it has been attributed to recurrently coupled anabolic and catabolic processes which, by creating and destroying chemical substances and/or physical states, prompt the impulse. The frequency of discharge under these circumstances is determined by the rate at which these processes occur and by the level or threshold at which they become effective. Furthermore the focus with the most rapid anabolic and catabolic build-ups is responsible for initiating the events of the heart beat.

When, for any reason, the sino-atrial node, the normal or primary pacemaker, is depressed, one of the secondary or tertiary foci take up its function. These subsidiary stations vary in their sensitivity. The order of their descending excitability is as follows: the uppermost, upper, middle and lower parts of the atrioventricular node, the atrial tissue, the branches of the atrioventricular bundle and the ventricular musculature.[9]

The rate of activity of the sino-atrial nodal tissue is determined mainly by the inhibitive influence of the vagus and the augmentative action of the sympathetic nerve fibers. This control is a direct and effective expression of stimuli which originate in various types of sensory end organs or at different levels of the central nervous system. In addition to the neurogenic factors, the activity of the primary pacemaker is influenced by circulating chemicals and hormones and by the physical characteristics of the blood. These factors exercise their effect directly on the sino-atrial nodal tissue itself or reflexly by stimulating various end organs.

The activity of the secondary and tertiary pacemakers is subject to all of these controlling influences in proportion to their inherent excitability. Under ordinary circumstances, the spontaneous discharge of these ectopic stations is prevented by the more rapid rate of activity which is generated by the primary or dominant pacemaker. However, under conditions of both health and disease perhaps in response to neurogenic, hormonal or other factors, a dormant focus may initiate a sporadic or intermittent competitive impulse or may remain unsuppressed and constantly functioning. These phenomena alone and in association with peculiar mechanisms of conduction account for the wide assortment of benign and complex arrhythmias which are observed clinically.[13]

Conductivity. A special conduction pathway does not exist in the atrium of the mammal. The cardiac impulse progresses slowly through the sino-atrial node and then spreads centripetally through the atrial syncytium at an average rate of 900 mm. per second. The wave front is reasonably uniform and its general direction is caudad, sternad and to the left with the postero-inferior area of the left atrium the last region to be activated. The atria are fully ac-

tivated 0.08 to 0.12 seconds after the initiation of the impulse.[18]

It is currently believed that a specialized conduction path does not exist between the sino-atrial and the atrioventricular nodes but that the activation process arrives at the latter area in the course of its natural spread through the atrial muscle. Here, the rate of transmission is relatively slow. The time required for conduction is estimated at approximately 0.05 second by which time the atria have completed their systole.

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is uniform at all times. Significant variations in excitability occur in both health and disease The most common example of this phenomenon is observed during the ordinary heart cycle.

Quite akin to conduction tissue the cardiac muscle develops an absolute refractory period upon responding to a stimulus This refractory period shortens with an increase in heart rate and lengthens with slowing as well as with stronger muscular contractions It is shortest in atrial tissue, intermediate in the ventricles and longest in nodal tissue in which it is subject to considerable variation The refractory period prevents a tetanic contraction from being initiated in the cardiac muscle in response to rapidly recurrent stimuli If the impulse occurs early in diastole, however, it may precipitate ineffective fibrillatory movements within the muscular mass

The Cardiac Contraction

Structural Components

The atria, ventricles and valves, each anchored in the fibrous framework of the heart, are the essential structural units involved in cardiac contraction

The fibrous base of the heart is formed by the fusion of the connective tissue fibers which surround the two atrioventricular ostia, the root of the aorta and the root of the pulmonary trunk These rings or annuli fibrosi reinforce the attachment of the valves The atria are fastened to the superior surface of the connective tissue rings of the mitral and tricuspid valves Both ventricles are fastened to the entire circumference of the fibrous skeleton [13]

The atrial myocardium is attached to the annuli surrounding the atrioventricular ostia The superficially distributed fibers encircle both atria or enter the interatrial septum embracing the atrial cavities in a figure eight pattern The deeper fibers are attached to one annulus and encircle one atrium.

The ventricular myocardium consists of interlacing muscle fibers which are partially separated from each other by fibroelastic connective tissue. Four muscular layers are distinguishable: the superficial sinospiral and bulbospiral, and the deep sinospiral and bulbospiral. The superficial bulbospiral bundles arise from tl left atrioventricular annulus and from the e' ternal investment for portions of both ver tricles as they wind toward the apex. Tl superficial sinospiral is the counterpart of th group The deep bulbospiral muscle fibers orig nate at the mitral ring and encase the basila portions of the left ventricle The deep sino spiral group encircle both the right and the lel ventricles after originating at the connectiv tissue of the tricuspid ring

The diameters of the individual muscle fiber vary but average 12 micra. The length is im possible to estimate because of extensive anas tomosis The surface layer of the fiber, th sarcolemma, contains the sarcoplasm whicl serves as a matrix for the myofibrils Opticall heterogeneous areas running along the lengtl of these latter structures give them a cros striated appearance The myofibrils contain th beaded myofilaments which function as th fundamental contractile unit of the heart.

The architecture of the ventricles suggests a division of the musculature into two precise functional components, the spiral and constrictor groups

Because of their configuration and distribution, contraction of the external and internal spiral muscles produces oppositely directed tensions and a shortening of the ventricular chambers along their longitudinal axis. Contrariwise, contraction of the deep myocardial bundles which rest between the spiral layers and encircle the base of the heart, reduces the over-all diameters of the ventricular chambers. These muscles actually function as constrictors They are more abundant in the left ventricle and interventricular septum than in the right ventricle This distribution accounts for the fact that left ventricular contraction, in contrast to right, is accompanied by a significant reduction in over-all diameter and limited longitudinal shortening.[14]

The Cardiac Cycle

Alternate periods of contraction and relaxation characterize cardiac action Atrial contraction develops with the initiation and spread of the impulse from the sino-atrial node. It takes the form of a gradual peristaltic wave during

which a variable quantity of blood is displaced into both ventricles. Pressures within the atrial chambers rise at the onset of this systole and gradually increase as the muscle completes its contraction The leaves of the atrioventricular valves begin to approximate one another as atrial systole progresses. This early movement facilitates the complete closure of the valves at the time of the isometric ventricular contraction

Excitation of the ventricle begins as atrial contraction is being completed, and the actual contraction of these chambers takes place approximately 0 075 second later. During the period of the isometric contraction of the ventricles, which is characterized by rising pressures and an unchanged volume within the chambers, the atrioventricular valves are completely closed and slightly ballooned into the atrial chambers. This accounts for a slight additional rise in atrial pressures which is encountered during this phase of cardiac action. Isometric contraction ceases when the ventricular pressures exceed those in the arterial tree and a volume of blood is ejected into the vascular system During the entire period of ventricular systole, the atria are relaxed and refilling.

The onset of ventricular relaxation develops with a drop of pressures below that of the arterial tree and is accompanied by the closure of the semilunar valves. During the isometric portion of this relaxation, the pressures fall below atrial values The atrioventricular valves then open and ventricular filling begins The initial transfer of blood from atria to ventricles is completed rather quickly, and before ventricular relaxation actually is terminated there is an equalization of pressures between the chambers with little or no flow of blood between them Atrial contraction now takes place displacing an additional quantity of blood into the ventricles and initiating another cardiac cycle.

Catheterization of the right and left heart chambers has revealed the range of pressures which are normally encountered during the cardiac cycle The systolic pressures in the right atrium vary from 2 to 4 mm Hg and in the left atrium from 4 to 8 mm Hg. The normal range in the right ventricle is from 20 to 30 mm. Hg and in the left between 90 and 140 mm. Hg. The diastolic pressure in the atria varies from −2 to +2 mm. Hg. In the right ventricle, they are recorded from 0 to 4 mm Hg and in the left from 2 to 10 mm. Hg[2]

The pressure in the central aorta varies with the cardiac cycle During ventricular ejection, blood enters the aorta at a rate faster than it can flow out through the capillaries The pressure, therefore, rises rapidly and then tends to level off as the rate of ventricular ejection falls below the speed at which the blood escapes through the capillaries The only arrest in this gradual decline is a rebound which develops immediately following closure of the aortic valve. The pressures in the pulmonary trunk undergo similar variations[2]

Mechanism of Contraction

Blood from the superior and inferior venae cavae enters the right atrium in linear and swirling currents and is forwarded into the right ventricle at the period of its rapid filling.

Three separate mechanisms are responsible for the ejection of blood from the narrow crescent-shaped cavity of the right ventricle: (1) The contraction of the spiral muscles constricts the ventricular chamber along its longitudinal axis by shortening the myocardial wall and displacing the tricuspid valve ring toward the apex (2) The concave surface of the myocardial wall and the convex interventricular septum move toward one another in a bellows-like action This is a most effective mechanism since it displaces a large quantity of blood while causing only a limited reduction in the chamber area (3) The contraction of the left ventricle probably causes an increased convexity of the interventricular septum thereby augmenting the bellows action This mechanism is significant only because slight movements of the interventricular septum enhance the basic efficiency of the bellows action.[16]

The ejection mechanism is accompanied by a movement of the right ventricular wall toward the apex which remains remarkably stationary. Rotation of the chamber, likewise, is minimal during contraction

The left ventricular cavity has a cylindrical contour. It is encircled by deep fibers which are situated between the spiral muscle l...

Contraction of the left ventricle results in a reduction in the diameter of the chamber and a shortening of the longitudinal axis. The reduction in the diameter of the cavity is the *primary action responsible for ejection*. It is *brought about by contraction of the deep constrictor muscle bundles*. The shortening of the longitudinal axis contributes only in a limited fashion to the total effort. Although this shortening results in a movement of the mitral valve ring toward the apex it causes little reduction in the distance between the root of the aorta and the apex.[15]

Teleologically, the right ventricle is admirably suited to the injection of large volumes of blood under normal pressures. It is not adapted to the development of high intraventricular pressures.

Contrariwise, the left ventricle is architecturally designed to function as a high pressure pump and is less capable of adapting itself to the ejection of large volumes of blood.

The Regulation of Cardiac Output

Cardiac output may be defined as the volume of blood ejected by either ventricle in a unit of time. It is usually expressed as cubic centimeters or liters per minute. Actually, the output is a function of the size of an individual. Accordingly, it may be expressed as the cardiac index which is the output in liters per minute per square meter of body surface.

Under normal circumstances, the output of the two ventricles per minute is the same and is equal to the total volume of circulating blood. However, in specific congenital and acquired lesions such as aortic insufficiency, septal defects and patent ductus arteriosus, the output of the two ventricles is unequal and differs from the total circulating volume.

The cardiac output is equal to the heart rate multiplied by the stroke volume, and of course may be increased or decreased by variations in one or both of these factors. Since stroke volume itself is determined by the arterial blood pressure, the effective filling pressure, myocardial distensibility and contractility, cardiac output actually is regulated by five discrete mechanisms.[8]

Heart Rate

Any increase in cardiac rate predominantly *foreshortens diastole and reduces the time for* ventricular filling. Under experimental conditions when a constant venous return is maintained, a more rapid rate produces an increase in output for a short period after which a new balance is struck and the output returns to its previous level. This results because of the smaller initial ventricular tension and length that develop with the decrease in diastolic filling time. Since cardiac oxygen consumption rises, and there is no actual improvement in output, the over-all effect of an increase in rate is detrimental.

Under the same experimental conditions, if venous pressure is maintained at a constant pressure, the decreased diastolic time has a minimal influence on ventricular filling, and the cardiac output increases in proportion to the heart rate. The mechanism for this response is believed to be a more rapid diastolic relaxation of the ventricle. The increase in cardiac output which accompanies an acceleration of rate requires a greater oxygen consumption than the increase which develops from an improvement in stroke volume.

Arterial Blood Pressure

An increase in arterial blood pressure momentarily reduces stroke volume. However, the retained volume of blood within the left ventricular chamber increases the initial length of the myocardial fibers and this functions to restore the output to normal. This is accomplished at the expense of greater oxygen consumption.

An increase of pressure in the pulmonary arterial system has a similar effect on the right ventricle.

Effective Filling or Venous Pressure

A positive gradient between the effective venous pressure (intravascular-extravascular pressure) and the right ventricle must be maintained at all times in both venae cavae regardless of body position or the volume or the distribution of blood in order to assure the return of blood to the heart. Under ordinary circumstances, a rise in central venous pressure will

induce an increased filling of the heart and will augment the output of first the right and then the left ventricle. However, if this increase is excessive, it will serve only to induce the accumulation of fluid in dependent tissues. Contrariwise, a negative pressure gradient will result in deficient diastolic filling. It is quite apparent, therefore, that the central venous pressure must be maintained between critical excesses in order to assure a normal cardiac output.

The exact means by which the central venous pressure is properly controlled remains to be clarified. However, it is quite likely that external compression of the veins by the skeletal muscles in the legs and the contraction of large venous reservoirs represent the major forces which regulate the central venous pressure to a level above that of the right atrium under various circumstances, most particularly alterations in position

Myocardial Distensibility

The diastolic volume of the ventricular chambers is determined by the effective filling pressure and the resistance to distention by the myocardial walls Viewed differently, myocardial distensibility may be defined as the diastolic volume per unit of effective filling pressure

Diastolic filling occurs in three phases (1) The rapid filling phase occurs at the very onset of diastole during which time the resistance to ventricular distention is at a minimum Actually, a progressive drop in pressure indicates that the ventricle expands more rapidly than the flow of blood, (2) the phase of diastasis during which the forces distending the myocardium are balanced by those opposing this stretching, (3) the phase of presystolic filling during which atrial contraction displaces the remaining blood, approximately one-third of the total quantity, into the ventricular cavity.

The distensibility of the ventricular chambers during these periods is under neural and hormonal control It is also affected by a number of other pertinent factors For example, the resting tension-fiber length relations of the relaxed myocardium suggest that the volume of diastolic filling is enhanced by augmented tension. As a further example, the release of interfascicular tension may regulate the onset of the very rapid ventricular filling which occurs during early diastole while myocardial viscosity may account for the resistance which ultimately develops to terminate that phase[15]

It is clear that any reduction in the inherent power of the myocardium to resist stretching enhances diastolic filling. This, of course, provides a mechanism whereby the stroke volume of the heart can be increased without changes in venous and arterial pressures

Myocardial Contractility

During the early portion of systole, the period of isometric contraction, the intraventricular pressure rises until it exceeds the arterial values Thereafter, blood is ejected from the ventricular chambers as the myocardial fibers shorten. This ejection continues as long as the fibers maintain adequate tension

The speed, vigor and completeness of the cardiac emptying is an expression of myocardial contractility. The basic nature of the contractile process develops from the functional characteristics of the individual fibers It is significantly influenced by four factors (1) Starling's law of the heart, (2) myocardial viscosity, (3) interfascicular tension and (4) the law of Laplace

Starling's law states that the energy released by the contracting fibers depends, in part, on the initial length of the muscle strips Otherwise viewed, contractility improves with large diastolic volumes In addition, there is ample evidence to suggest that the amount of energy released in contraction is enhanced when the myocardial fibers are placed at various degrees of stretch beyond their initial or resting length. Such dynamic alterations in length or volume produce additional tensions which are superimposed on the already developed resting quantity This mechanism of improving contractility probably functions during the period of isometric contraction when the intraventricular pressures rise but the fibers do not shorten.

Myocardial viscosity refers to the internal resistance or friction that develops in response to sudden or rapid shortening. A portion of the

energy developed in contraction is utilized to overcome this resistance Actually, the amount of energy lost is proportional to the speed and extent of the fiber shortening. Based on the concept of myocardial viscosity, it appears that myocardial contraction is less wasteful when it functions at a large *systolic dimension*

The myocardial fibers of both ventricles are *oriented in at least three different directions* Part of the energy developed in the contractile process of the heart muscle is utilized in applying tension to the tissue connections between these various layers The amount of energy wasted as interfascicular tension increases as muscle shortening progresses or as systolic ejection becomes more complete As previously indicated, interfascicular tension probably *reaches a minimal value at some point in* diastole Again, the implication exists that the greatest economy of contraction takes place at large systolic dimensions[14]

Whereas Starling's law and the concepts of myocardial viscosity and intrafascicular tension suggest that more energy is released and less is wasted in contraction when the diastolic and systolic volumes are great, the law of Laplace (pressure-tension 'radius) suggests that the tension required to sustain a specific interventricular *pressure diminishes as the radius* of the chamber is reduced Thus, this factor *compensates for the energy loss which develops* through myocardial viscosity and interfascicular tension when the muscle fibers shorten

Essentially, it is an interplay of the four factors as discussed previously, they determine the fundamental characteristics of myocardial contractility and its influence on cardiac output[16] The ideal functional environment permits the greatest amount of work to be accomplished by the heart muscle per unit of oxygen consumed. It is quite clear that in obtaining an identical output a limited muscle shortening in the presence of a large diastolic *volume* is *more* economical than a marked shortening for a small diastolic volume. It is *also clear that* the basic economy of contraction can be improved by any mechanism which reduces internal *resistance* and decreases frictional and interfascicular energy loss. Impressive evidence *indicates* that both neural and hormonal influences may serve to activate such mechanisms.

Myocardial Metabolism

The rhythmic contractions of the heart represent the fundamental movements of life. They propel the blood into the pulmonary and systemic circulations, which is required for the metabolic needs of the tissues Unfortunately, only limited knowledge exists concerning the biochemical processes which are responsible for the characteristic repetitive shortening of the cardiac muscle fibers.

Functionally, the heart is a pump and differs from skeletal muscle which serves as a *contractile lever It differs* also in its autogenic excitation, inherent rhythmicity and autonomic control However, myocardial fibers have many anatomic and functional characteristics in common with skeletal muscle including color, shape, cross striations, and the speed, vigor and duration of contraction Furthermore, experimental evidence appears to indicate that both the heart and skeletal muscles derive *energy for contraction in the same manner from* very similar types of fuel

Biochemically, the heart, like other organs, must receive an adequate supply of raw materials from the capillary circulation *including* substrates, oxygen and enzymes Cardiac work is peculiarly dependent on aerobic metabolism. The structure reflects this dependence in its copious arterial channels, large total blood flow and small capillary diffusion distances.

Having received energy-containing fuels, the heart must degrade them by oxygenation in order to release the available energy It must then capture and store the energy and convert it to useful work on demand Thus, the heart *is an energy-producing and utilizing structure*.

Myocardial metabolism refers to the sum of the chemical changes which *occur within the* muscle mass of the organ The essential phases of cardiac metabolism are (1) energy production and (2) energy liberation[11] The key elements in the metabolic process include (a) energy-containing fuels, (b) energy carriers, (c) muscle contractile elements (proteins) and (d) various ions, hormones and enzymes.[12]

Energy Production

Energy-containing fuels. Carbohydrates are the basic and primary energy-containing fuels utilized by the myocardium. The human heart uses glucose, lactate and pyruvate. The extraction and usage of these substances are functions of their coronary artery blood concentrations. Until certain upper arterial blood values are exceeded, the extraction increases as the concentration rises. At normal levels, glucose and lactate are used in approximately equal quantities. However, the total aerobic metabolism of glucose, lactate and pyruvate accounts for only 35 per cent of myocardial oxygen consumption. Obviously, this implies that the heart also utilizes noncarbohydrate substances as sources of energy.

Catheterization studies indicate that the heart utilizes considerable quantities of noncarbohydrates including fatty acids, amino acids and ketone bodies In the postabsorptive state, these materials double the contribution of the carbohydrates to the oxidative metabolism of the heart. Furthermore, the exceptional contribution of fatty acids to the oxygen use of the heart which takes place after a high fat diet suggests that fat itself is stored in the heart muscle. The exact role of the lipids in myocardial metabolism is unknown It has been theorized that the unesterfied fatty acids are utilized as a source of energy and that the phospholipids help to maintain contractility It is also believed that the transport and usage of these substances is under hormonal control.

Ketones are utilized in direct proportion to their arterial concentration and in inverse proportion to the amount of available carbohydrate The human heart extracts large quantities of amino acids from the coronary blood. There is no evidence, however, that these substances are stored Amino acids may form glycogen or nitrogenous compounds, or may be oxidized to some members of the citric acid cycle.

The avidity of the heart for, and its versatility in, utilizing carbohydrates and noncarbohydrates is an important safety factor. It is likely that the utilization of these materials is regulated entirely by their relative availability and the functional capacity of specific enzyme systems.

Energy carriers. The glucose which is delivered to the myocardial cells from the coronary circulation is converted to glucose-6-phosphate through phosphorylation and under the influence of glucokinase. Each of these molecules may be incorporated into glycogen or may form two identical molecules of pyruvic acid. In the course of normal aerobic catabolism, the pyruvic acid molecules are eventually oxidized to carbon dioxide and water with the release of most of the energy required for cardiac work.

Pyruvic acid is first quickly transformed to acetyl coenzyme A which, in combination with oxalacetate, forms citric acid Thereafter, as the result of the tricarboxylic acid cycle, two molecules of carbon dioxide and associated hydrogen atoms are removed by oxidative reactions In addition, the oxalacetate is regenerated so that it again may mesh with acetyl coenzyme A and thereby reinstitute the cycle.

The net result of the complete cycle is the oxidation of 3-carbon pyruvate to 3 molecules of carbon dioxide and the release of the energy contained in the carbon-to-carbon links The released hydrogen atoms are passed to flavoproteins and cytochromes which act as carriers. The energy derived from the carbohydrate substrate is released to a high-energy phosphate bond

Thereafter, in a series of complex biochemical maneuvers the energy which has been liberated is captured as adenosine diphosphate (ADP), or adenosine triphosphate (ATP) The synthesis of ADP results when nucleotide adenylic acid combines with one high-energy phosphate group. The synthesis of ATP is localized in the mitrochondria of the myocardial cells and results when the nucleotide adenylic acid joins with two high-energy phosphate groups.

Phosphocreatine, formed from a combination of creatine with one high-energy phosphate group also acts as an energy carrier and releases its group to form adenosine diphosphate.

Energy Liberation

Muscle contractile elements The contractile elements consist of actin, myosin, their conjugate actomyosin and various ions particularly

potassium and magnesium[17] Neither actin or myosin will contract independently. However, actomyosin a combination of these two substances, will contract in the presence of potassium and magnesium ions and ATP.

Actin is a long continuous thread-like protein It exists as both G-actin and F-actin The former is unstable and is polymerized to F-actin in the presence of magnesium, ATP and myosin This essential feature of the contraction process is accompanied by a degradation of ATP to ADP and the release of a high-energy bond to the actin molecule.

Myosin has a relatively short molecular form. Usually bound to magnesium it also has a marked affinity for potassium and calcium A single molecule is composed of heavy and slight meromysin molecules in a 1:2 ratio The heavy molecules link myosin to actin and have a marked capacity to attract ATP The folding of the light molecules appears to be responsible for muscular shortening or contraction

The complete chain of events in the process of muscular contraction is not fully recorded The essential features appear to be as follows In the resting muscle, the dissociated proteins actin and myosin are kept apart by the intracellular potassium ions. With depolarization, the cell membrane becomes permeable to potassium. The fall in the intracellular concentration of this ion permits the proteins to join and form actomyosin to which adenosine triphosphate is promptly absorbed The terminal phosphate of ATP is apparently released directly and supplies the actomyosin with the energy for the physical change which results in a folding or shortening of this contractile protein

During repolarization potassium re-enters the cell Adenosine triphosphate is regenerated from the residual dephosphate, and its high-energy phosphate bond is restored. The phosphorus is obtained in the enzymatic oxidation of carbohydrates or from stores of phosphocreatine. Actomyosin now is separated from the adenosine triphosphate and actin from myosin because of the increase in the concentration of intracellular potassium and the restoration of ionic equilibrium.

Some doubts have been recorded concerning these concepts of muscle contraction. Under certain conditions of laboratory investigation, the failure to demonstrate a decrease in ATP concentrations during the first phase of contraction suggests that the mechanism involved in the transfer of energy is not completely understood and that this substance may not be the actual unit responsible for the source of energy Furthermore, additional information concerning the structure of contractile proteins and their function may lead to a considerable extension of the current concept regarding their role in muscle shortening.

Metabolic Disturbances

Theoretically, disturbances in myocardial metabolism are divided into those of energy production, and of energy utilization and liberation The intricacies of the problem, however, and the limitations of present investigative technics are such that these phases of metabolism cannot always be separated. Furthermore, the disturbances may or may not be accompanied by an alteration in the mechanical efficiency of the heart

Animal investigations and human studies, limited mainly to post-mortem tissues, have been carried out in congestive heart failure and in myocardial infarction. These suggest the existence of abnormalities in the production, the release and the utilization of energy. However, the applicability of these observations to the living myocardium remains an open question There is no evidence to suggest that an inadequacy of energy-containing fuels or of accessory items such as ions or enzymes is a responsible mechanism for the development of congestive heart failure except in starvation or specific deficiency diseases such as beriberi. In the latter instance, a lack of thiamine chloride may interrupt the oxidative process of pyruvate to acetyl coenzyme A.

On the other hand, the belief that depressed energy production is responsible for decompensation is supported by observations of glycogen phosphorus and phosphocreatine concentrations in the myocardium.

A depletion in myocardial glycogen and a rise in lactic and pyruvic acid blood concentrations has been observed in patients with congestive heart failure and in those with myocardial in-

farction. Although it is clear that these changes are related to anoxemia there is no evidence that the local oxygen deficiency is of such a magnitude as to precipitate the need for anaerobic metabolism. Furthermore, consideration must be given to the view that these disturbances in the glycogen cycle follow rather than initiate the heart failure.

Additional evidence of abnormal energy production is provided by the observation that the trichloroacetic acid soluble phosphorus fraction (believed to represent the quantity bound in phosphocreatine, hexosephosphate and adenosine triphosphoric acids) is reduced in the cardiac muscle of those who succumb to congestive heart failure. Finally, the decreased concentrations of creatine in the myocardium of decompensated hearts also has served to support this view. The creatine values are thought to represent a significant decrease in the availability or concentration of phosphocreatine which is an immediate source of energy for muscular contraction

Significant but indirect evidence emphasizes the possibility that the metabolic fault leading to mechanical inefficiency of the heart resides in energy liberation and utilization rather than in energy production This defect theoretically could originate in the contractile proteins or in the efficiency of the release of the high-energy phosphorus bond. Precise experimental work implies that the physical or molecular structure of actomyosin and its precursor proteins is markedly altered in animals with cardiac decompensation However, there is no conclusive indication that this change in form, which produces decreased viscosity, results in the actual development of failure in humans.

Autopsy studies record a decrease in the myocardial potassium concentrations in patients who suffered from cardiac failure. This abnormality has been found to be associated with an increase in the sodium concentration so that the sum of the two ions remains comparable to the normal heart. Since these substances appear to regulate the phosphorylation of adenosine monophosphate (AMP) and adenosine diphosphate (ADP) to adenosine triphosphate (ATP), and of creatine to phosphocreatine, alterations in their concentrations must have a bearing on the utilization of energy. Actually, phosphorylation of creatine is enhanced when the potassium ion concentration is between 50 and 200 mEq./L. On the other hand, the conversion of AMP and ADP to ATP is inhibited when sodium concentrations are greater than 35 mEq./L. Accordingly, the combination of low potassium and high sodium concentrations would significantly interfere with the transfer of energy and consequently with myocardial contraction.

Summary

An understanding of the principles governing the function of the heart in normal individuals is a requirement for a proper interpretation of the changes brought about by disease. The heart functions as an automatic phasic pump with the phyisologic obligation of circulating blood in a quantity which is adequate for tissue needs The output of this organ is determined by its rate and stroke volume. Normally, the frequency of the cardiac contractions is regulated by the rate of discharge of the sino-atrial node which in turn is influenced by the action of the sympathetic and parasympathetic nerves. When the heart rate is constant, the stroke volume is determined by the venous return and the effective filling pressure. Evidence is accumulating that the stroke also is regulated by factors which affect ventricular distensibility and contractility. These functional characteristics of the myocardium are under the influence of a multitude of neural and hormonal controlling influences Finally, the basic factor which determines the efficiency of the pump mechanism resides in the myocardial metabolic processes. In this area, early and developing knowledge is clarifying the energy cycle which assures effective contraction

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Section II

EVALUATION OF CARDIOVASCULAR PHYSIOLOGY

— 4 —

Clinical Examination, Including History and Physical Findings in Cardiovascular Disease

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THE symptoms and signs which can be elicited in patients with cardiovascular disease are particularly valuable in delineating the physiologic disturbances of cardiovascular function In this chapter, we will discuss those symptoms and signs which may be of cardiovascular origin and will relate them insofar as possible to the disturbed physiology portrayed Many times the symptoms are unassociated with cardiovascular pathology and are the result of physiologic effects ordinarily neither dangerous nor disabling. At other times, cardiovascular pathology has caused no physiologic aberrations sufficient to produce recognizable symptoms or, less commonly, detectable signs The subjective manifestations will first be considered without particular precedence as to importance or frequency

Subjective Manifestations: History

Palpitation

One of the most common symptoms complained of by patients concerned about their hearts is increased awareness of the heart beat or *palpitation* It may be associated with a regular or irregular rhythm, a fast or slow rate, an abrupt or gradual onset and offset and it may be described as pounding, skipping, thumping or fluttering of the heart When palpitation is associated with a regular rhythm and a normal rate, it suggests cardiac enlargement with a forceful apical impulse, and when associated with abnormally slow rates, it suggests an advanced degree of heart block When associated with a regular rhythm and rapid rate with gradual onset and offset, it suggests a sinus tachycardia, whereas with an abrupt onset and offset a paroxysmal tachycardia is likely to be the cause Palpitation associated with an irregular rhythm and slow or normal rate is usually due to ectopic beats When these disappear with an increase in heart rate, they are usually benign, and when persistent suggest the presence of heart disease Palpitation with a rapid irregularity occurs with atrial fibrillation which is often paroxysmal Atrial flutter may cause palpitation with a rapid or normal rate and a regular or irregular rhythm.

Dyspnea

Dyspnea is subjective difficulty in breathing. In mild form, it may not be accompanied by objective evidence of breathlessness, but when severe it is associated with obvious respiratory difficulty [1-8] Dyspnea may occur in pulmonary insufficiency, anemia, certain neurologic and psychiatric disorders and various metabolic and endocrine disturbances When due to heart disease, it usually appears in association with ease of fatigue and increasing weakness as the earliest triad of symptoms suggesting heart failure

The essential feature of cardiac dyspnea is pulmonary vascular congestion Such pulmonary congestion may be secondary to: (1) myocardial (left ventricular) failure or (2) mechanical obstruction Both types are heralded by dyspnea with exertion which is slowly or rapidly progressive and may or may not be episodic The progression of dyspnea may be useful in differentiating myocardial failure from mechanical obstruction. One of the most important differential features is paroxysmal noc-

turnal dyspnea. This is noted in left ventricular myocardial failure from hypertensive heart disease, coronary artery disease, mitral insufficiency or aortic valve disease. Paroxysmal nocturnal dyspnea is due to the gradual accumulation of blood in the pulmonary vascular system and usually occurs three to four hours after the patient has retired for the night The horizontal position facilitates venous return from the viscera and lower extremities; blood slowly collects in the lungs because of a slightly lesser output from the left ventricle than from the right. This gradual accumulation of blood, usually followed by extravasation of fluid into interstitial spaces and alveoli, causes dyspnea and forces the patient to sit up in bed with his feet over the side or to stand and walk.

In contrast to paroxysmal *nocturnal* dyspnea is acute paroxysmal *exertional* dyspnea encountered primarily in patients with mechanical obstruction. Mitral stenosis and restrictive disease of the heart and great vessels are the principal causes of the mechanical obstruction. FIGURE 1 outlines the similarities and differences between the progression of dyspnea occurring with myocardial failure and with mechanical obstruction.

The pathogenesis of cardiac dyspnea is complex. Fluid accumulation in the lungs is important. Restriction of left ventricular inflow, obstruction to left ventricular outflow or inability of a weak left ventricle to expel completely the blood returned to it via the pulmonary veins leads to an increased fluid volume in the pulmonary vascular bed. This increased volume makes the lungs more rigid, limits respiratory excursions and results in shallow respirations. Transudation of fluid into the tissues further increases the rigidity of the lungs and hinders alveolo-capillary gas exchange. Thus, as breathing becomes more shallow, the respiratory rate must be increased to maintain adequate gas exchange.

Nervous and humoral mechanisms, capable in themselves of producing dyspnea, may be accessory factors in dyspnea due to heart failure The occasional overloading of the circulation through the injudicious use of salt and fluids in the presence of a failing left ventricle or obstruction to left heart outflow may also precipitate dyspnea through increased pulmonary fluid volume.

When paroxysmal cardiac dyspnea is accompanied by wheezing and rhonchi, it is termed cardiac asthma. The wheezing is prob

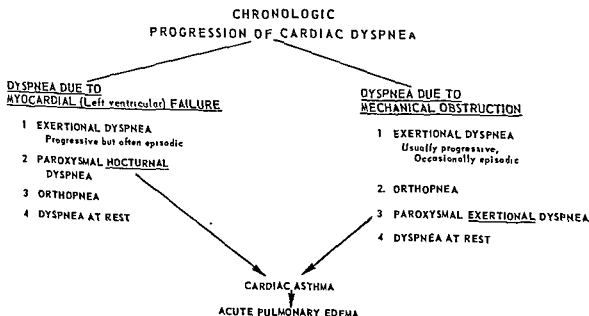


FIG. 1 —Similarities and differences between the progression of dyspnea occurring with myocardial failure and with mechanical obstruction

ably due to bronchial obstruction as a result of congestion and edema of the bronchial mucosa and possibly also to *bronchospasm*. *If*, as a result of the increase in pulmonary congestion, the pulmonary capillary pressure becomes elevated for a sufficient period of time, pulmonary edema will develop. Wet, frothy cough, at times progressing to bloody or "salmon-tinged" sputum, are late developments.

Acidotic respiration, resulting from certain metabolic mechanisms, is characterized by deep rapid breathing, but is *not associated* with the subjective distress seen in cardiac dyspnea.

In the unusual instance in which right heart failure precedes left heart failure, there should be no dyspnea of cardiac origin. However, practically all instances of pure right heart *failure are caused by pulmonary disease* which causes dyspnea long before any significant cardiac involvement ensues. In pulmonary heart disease, therefore, dyspnea is usually an early symptom related to the *pulmonary* insufficiency. The right heart failure in no way causes dyspnea.

In congestive heart failure due to chronic constrictive pericarditis, dyspnea usually occurs only on exertion, presumably due to inability to increase the stroke output of the heart. Sometimes, dyspnea at rest and pulmonary congestion are also apparent and are related to restriction of pulmonary vein inflow by the nondistensible left ventricle. Occasionally, an asymptomatic chronic nonconstrictive *pericarditis becomes acutely symptomatic by* virtue of a small pericardial effusion causing cardiac tamponade in the presence of the inelastic pericardium.[5]

The rare paradoxical dyspnea in the upright position, relieved by lying down or present only with certain positions, and abruptly relieved by changing position, may be due to a ball-valve thrombus or other tumor of the right or *left atrium intermittently obstructing* the tricuspid or mitral valve. Care should be taken to search for the rumbling diastolic murmur which appears and disappears with position changes and is heard over the tricuspid or mitral areas.

Ease of Fatigue and Weakness

The ease with which an individual tires is often a measure of physical fitness or physical tone. When the symptom is progressive and associated with breathlessness, it may represent one of the earliest developments of cardiac weakness. The *physiologic explanation* usually given for this symptom complex is inability of the heart to increase the cardiac output to meet the demands of effort. Increased oxygen desaturation of venous blood and accumulation of metabolites results from insufficient cardiac output and is probably physiolog*ically implicated in the fatigue sensation.*

Weakness, when associated with overt manifestations of congestive heart failure, is more chronic and tends to become manifest at a later date than ease of fatigue. When weakness is prominent, fatigue is ever present.

Dyspepsia, Abdominal Pain and Systemic Vascular Congestion

Dyspepsia and upper abdominal pain are prominent symptoms in congestive heart failure related primarily to the development of systemic vascular congestion.

Dyspepsia includes the symptoms of early satiety, anorexia, abdominal bloating and upper abdominal distress or pain. When cardiac in origin, it is an *expression of abdominal* visceral vascular congestion, its principal objective manifestation being a swollen, tender liver and occasionally an enlarged spleen. Systemic vascular congestion is the result of either right ventricular myocardial failure or mechanical obstruction in the systemic veins *or right atrium, or at the tricuspid* valve. Because of the tremendous expansibility of the peripheral venocapillary bed, vascular congestion and its attendant symptoms need not be accompanied by measurable increases in the peripheral venous pressure.

Edema

Systemic vascular congestion is associated with edema, often especially noted in dependent parts of the body as a swelling which pits on pressure. Concomitant with, or independent of, *the dependent edema, there may*

be effusions in the body cavities, ascites which may add to the dyspeptic symptoms and hydrothorax which may cause or aggravate dyspnea. The edema of cardiac origin results primarily from sodium retention and from congestion of the systemic venocapillary beds. The pathogenesis of cardiac peripheral vascular congestion and edema are discussed in greater detail in Chapter 12.

Chest Pain

Chest pain is one of the most frequent complaints a physician must evaluate. Most patients presenting themselves with this complaint are fearful that they have heart disease Fortunately, a significant number do not. It is as important to determine this fact as it is to make the correct diagnosis of cardiac disease

Chest pain may arise from structures within the chest or from the chest wall itself. The three classes of chest pain to be differentiated are: (1) those arising from the lung and pleura, (2) from the chest wall and (3) from the heart and great vessels

Those conditions arising in the lung and producing pleuritic pain do so by extension of the process to involve the parietal pleura, since neither the lungs nor the visceral pleura possess pain fibers The parietal pleura, however, is quite sensitive to pain. The afferent pain fibers originating in the pleura are small branches of the intercostal nerves Pleural pain is, therefore, usually sharply localized to the area of the skin immediately overlying the involved pleura The outstanding characteristic of pleural pain is its sharp piercing quality and its aggravation by cough or deep inspiration

Pain from the chest wall may be ligamentous, muscular or skeletal, and is referred to the corresponding somatic sensory dermatome as discussed below Clinically important differential features of this type of pain are the initiation, aggravation or relief of pain with changes of position, or association of pain with local joint or muscle disease

An appreciation of the innervation of the heart and great vessels of the thorax will provide a better understanding of the anatomic sites in which pain originating in certain structures will be experienced

Nerve pathways by which pain is conducted from the heart are to be found in periarterial plexuses in the adventitia of the coronary arteries, and the superficial and deep cardiac plexuses. Conduction is by way of the sympathetic nerves to the first five thoracic sympathetic ganglia from which they enter the spinal cord by the white rami joining the upper four or five dorsal spinal nerves The vagus and phrenic nerves may also carry pain impulses from the heart in some instances. Pain fibers are also carried from the cardiac plexuses via the superior, middle and lower cervical cardiac nerves to the cervical sympathetic ganglia and to the upper thoracic ganglia The pain fibers of the parietal pericardium are carried by the phrenic nerves. The visceral pericardium has no pain fibers.

The sensory fibers from the heart and the somatic sensory fibers from the precordium, inner aspect of the arm, and fifth finger join before entering the spinal cord. Because they lie together in the same spinal cord segments (D1–D5), there is referral of cardiac pain to these areas of the body surface (dermatomes).

The most commonly encountered cause of chest pain of cardiac origin is the *anginal syndrome*. This is an abnormal physiologic state in which the myocardial blood supply is inadequate to meet the needs of the myocardium under the conditions obtaining at a given time. The resulting myocardial ischemia is frequently associated with characteristic pain. It may be provoked by an absolute diminution of coronary blood flow, as in obstructive lesions of the coronary arteries, or by increased cardiac need for blood disproportionate to the available supply, as in severe anemia or tachycardia. It is still not entirely clear just how this diminution in coronary blood flow precipitates the pain Several theories have been propounded including anoxemia of the myocardium, accumulation of abnormal metabolites within the ischemic myocardium and painful impulses arising from the walls of the coronary vessels themselves

The major manifestation of the anginal syndrome is chest pain, which in its typical form

is readily recognized. The pain is usually precipitated by exertion, excitement or other strong emotional experience, a heavy meal or exposure to cold. The left precordium, or more commonly the sternal region, is the site of the pain. Occasionally, it is felt more prominently near the lower end of the sternum or in the epigastrium In such instances the association of flatulence and nausea may lead the patient and the physician to believe that the pain originates in the gastrointestinal tract. It is a common occurrence for the pain to radiate to the left side of the neck, left shoulder and down the inner aspect of the left arm The radiation may be to both shoulders and arms or to the right side alone. More rarely the pain may radiate to the jaw or teeth The occasional radiation of pain to the face is accounted for by the passage of a few of the sensory fibers from the heart through the superior cervical ganglion to the trigeminal ganglion

The character of the pain varies and to some extent depends on the patient's ability to verbalize the subjective experience It may vary in intensity from a sensation of slight heaviness or fullness to severe, excruciating, crushing retrosternal pain If the pain has been experienced during activity, the patient usually is compelled to rest before relief is obtained

Because the ischemia provoking the pain is transient, the duration is usually brief, rarely lasting more than three minutes The striking relief of the pain afforded by sublingual administration of nitroglycerin is of diagnostic as well as therapeutic significance

In *myocardial infarction* the pain has a similar distribution but usually is more severe and of longer duration. The pain of myocardial infarction is thought to result from the profound ischemia leading to necrosis of part of the muscle The pain of myocardial infarction occasionally may last for days and is usually unrelieved by nitroglycerin. There may be associated nausea, vomiting, diaphoresis and an ashen-grey cyanosis.[5]

A clinical syndrome of cardiac pain intermediate between angina pectoris and myocardial infarction has been described and has been given the designation "coronary failure."[4] The physiologic explanation for the pain is severe but reversible myocardial ischemia, and therefore appears to represent a quantitative variant of the anginal syndrome.

Pain associated with *acute pericarditis* is usually substernal or located immediately to the left of the sternum and is frequently described as a dull ache, but occasionally may be so severe as to be almost indistinguishable from myocardial infarction. The pericardium is poorly supplied with pain fibers, only the lower parietal pericardium being supplied with a few pain fibers carried in the phrenic nerve. The pain experienced in pericarditis is due largely to involvement of the adjacent pleura. When the central portion of the diaphragm is involved, the pain may be referred to the shoulder because the phrenic nerve which innervates this portion of the diaphragm enters the middle cervical segments at the same level as do the somatic sensory fibers of the neck and shoulder

Severe precordial pain is also encountered as a primary symptom in the *postcommissurotomy*, the *postcardiotomy*, and the *postmyocardial infarction syndromes*[2, 9] These syndromes are believed to be the result of auto-immune antigen-antibody reactions occurring in certain susceptible patients. Pericarditis is an important part of the clinical picture and probably is the explanation for the chest pain.

Dissecting hematoma of the aorta (dissecting aneurysm) is characterized by the sudden onset of severe, ripping, tearing, upper retrosternal pain with radiation in the direction of the dissection. The dissection commonly originates one to two inches above the aortic ring, which accounts for the upper retrosternal site of the initial pain Its subsequent radiation is dependent on the direction and extent of the dissection and on the interference with the blood supply to other organs *Afferent* pain fibers of the thoracic aorta take a pathway to the spinal cord essentially the same as those for the heart Hence, the anatomic sites for referred pain are approximately the same as for cardiac pain.

Aneurysms of the aorta due to syphilis produce pain by pressure of the aneurysmal sac on adjacent nerves or by bone erosion. Aneurysms may extend forward to erode the ster-

num or ribs causing anterior chest pain, or they may extend backward and erode the vertebrae with resulting pain in the back.

The pain of *pulmonary embolism* may be difficult to distinguish from that of myocardial infarction It has been suggested that myocardial ischemia may occur in pulmonary embolism as a result of hypoxemia or reflex coronary vasoconstriction.

The pain occurring in some patients with *pulmonary hypertension* may closely resemble the pain of angina pectoris. This pain has been ascribed to right ventricular hypoxemia secondary to compression of small coronary vessels by the high pressure within the right ventricular cavity

Objective Manifestations: Physical Findings

Since the heart is a three-dimensional organ within the chest cage, one first notes the external characteristics and functional integrity of the thorax. Asymmetry of the thorax may result from heart disease or may be an etiologic factor producing heart disease. A localized precordial bulge signifies enlargement of the heart at a very early age and is usually seen in congenital lesions with considerable right heart enlargement, or in rheumatic mitral valve disease developing before the fifth year of life. Pectus excavatum or kyphoscoliosis are thoracic abnormalities which may lead eventually to the development of pulmonary heart disease.

Inspection

Many significant physiopathologic observations are possible from simple visual study of the patient. A history of dyspnea may frequently be accompanied by objective evidence of respiratory difficulty. Diffuse or regional cyanosis may be observed as well as clubbing of the fingers and toes, venous distention, edema of soft tissues, and abnormal bulging, retractions or pulsations of the precordium or peripheral vessels Dusky redness of the tip of the nose, cheeks and chin occurs in mitral stenosis. Obstruction of the superior vena cava from thrombosis, tumor, infection or aneurysm is associated with cyanosis of the head and neck, edema of the neck (Stokes Collar) and dilated superficial veins of the thorax, with the abnormal characteristic of filling from above. These superficial veins have become collateral circuits of venous drainage from the upper extremities to the inferior vena cava and right heart, thus circumventing the obstructed superior vena cava.

Distended veins of the extremities, when raised above the level of the right atrium, will empty to the point representing the approximate venous pressure A pulsation may be seen at this level which may be centrifugal (coming from the heart) or centripetal (coming from the capillary bed). Centrifugal pulsations may represent tricuspid insufficiency from heart failure much as does a pulsating liver. Centripetal pulsations suggest a dilated capillary bed such as is seen in aortic insufficiency, hyperthyroidism or the vasomotor changes associated with fever. Differentiation of centripetal from centrifugal venous pulses is simply accomplished by digital compression of the vein proximal and distal to the point of pulsation.

Arterial pulsations are commonly observed in the carotids in association with cardiac overactivity and aortic insufficiency. Sinuous arterial pulsations in the extremities are associated with arteriosclerosis, loss of elasticity and lengthening of the peripheral arteries.

Pallor of the skin, erythremia, petechiae and telangiectasia may all be important signs suggesting or explaining heart disease.

Cyanosis occurs when there are five or more grams of reduced hemoglobin per 100 cc. of capillary blood in the dilated peripheral capillaries. It is best seen where subpapillary venous capillary plexuses are superficial and numerous. The underlying etiology may be heart disease, pulmonary disease, venous obstruction, polycythemia, drugs or blood stagnation, and may be mimicked by the now uncommon argyria or by capillary telangiectasia such as is seen in certain cases of functioning carcinoid. Cyanosis may be constant or present only under certain circumstances such as exertion. In addition, it may be generalized or localized to one part of the body, and it may be associated with a warm or cool skin.

Generalized cyanosis may result from decreased arterial oxygen saturation (warm or central cyanosis) or increased oxygen utilization (stagnation, peripheral or cool cyanosis) Decreased arterial oxygen saturation may be due to shunting of venous blood to the arterial circuit in the heart, lungs or great vessels, or to impairment of oxygen diffusion from the alveoli to the capillaries Increased utilization of oxygen peripherally may be due to stagnation from increased venous pressure or vasomotor collapse Intermittent cyanosis of generalized nature is manifested with exertion and implies reversal of flow in a shunt which at rest is left to right but with increased right heart pressure during exercise becomes right to left. A cardiac output unable to increase with the demands of exertion may also be associated with generalized cyanosis

Localized or differential cyanosis is seen in *superior vena caval obstruction* with cyanosis of the head and neck, in interruption of the aortic isthmus, the pulmonary artery being continuous with the abdominal aorta and resulting in cyanosis of the feet and legs and in localized venous obstruction with cyanosis occurring distal to the obstruction

Clubbing of the fingers and toes is often associated with cyanosis It is seen as a bulbous swelling of the soft tissues of the terminal phalanges and as a convex curvature of the nails resembling watch crystals The pathogenesis is unclear Microscopically, proliferation and dilatation of venules and capillaries are observed. Clubbing is seen in congenital heart disease with cyanosis, chronic pulmonary disease and in bacterial endocarditis as an early sign when heart failure and cyanosis are absent

Palpation of the precordium may disclose the presence of impulses or thrills Over arteries, one may detect thrills and note the characteristics of the pulse wave, palpation over the lungs may indicate changes in tactile fremitus or the presence of thrills of vascular aneurysms or arteriovenous fistulae Precordial impulses may be systolic or diastolic in time and may occur in various precordial areas characteristic for specific aberrations [3]

Thrills are the tactile equivalent of murmurs and are due to the turbulence of blood flow Turbulence of flow is the result of (a) change in velocity of flow across a stenotic area or from a smaller to a larger (dilated) chamber, (b) a decrease in blood viscosity (anemia) and (c) reversal of blood flow into a retrograde chamber moving against forward flow. The more important thrills are indicated in TABLE 1 in the column "associated signs"

The *arterial pulse*, through alterations in its volume and its contour, gives information as to the outflow of blood from the heart and the peripheral resistance to that flow

The pulse volume may be accentuated by increased stroke volume from exercise, fever, thyrotoxicosis, aortic insufficiency, decreased peripheral resistance or arteriovenous fistula. The pulse volume may be decreased by reduced stroke volume from aortic stenosis, mitral stenosis or insufficiency, heart failure, sclerosis of the aorta, tachycardia or increased peripheral resistance

Alterations of contour are more diagnostic than alterations of volume The contour may be abnormally shallow or steep and there may be accentuation, prolongation or reduplication of peaks normally present Thus the "water-hammer" pulse of aortic insufficiency has a rapid rise, a sharp deep fall (*magnus-brevis*) and a volume which may be normal or increased These qualities become more apparent with elevation of the arm because such elevation increases the sharp fall or collapse through gravity, and because elevation tends to straighten the arterial column from the aorta to the radial artery This same direct extension from the aorta to the femoral artery accounts for the sharp rise and fall of the femoral in contrast to the radial pulse

In contrast to the *magnus-brevis* pulse is the *parvus-tardus* pulse of aortic stenosis which is associated with reduced or extended stroke output and increased peripheral vascular resistance The rise and fall of the pulse wave is more gradual, and the volume is often reduced with a prominent anacrotic notch and delay in propagation of the pulse wave along the peripheral arteries

Percussion

Percussion is used to delineate the borders between air-containing and solid organs Dull-

TABLE 1.—*Outline of Characteristics of Common Heart Murmurs*

Physiologic abnormality	Characteristics of the Murmurs: Time	Pitch	Quality	Special characteristics	Maximum loudness	Radiation	Body position best heard	Associated signs
Mitral stenosis	Mid diastole and presyst	Low	Rumble		Apex	0	Left lateral decubitus	Accentuated P_2, split P_2; Accentuated M_1, opening snap
Tricuspid stenosis	Mid-diastole and presyst	Low	Rumble		5th i s lt parasternal	0	Left lateral decubitus	Normal P_2
Aortic stenosis	Systolic	High	Coarse	Crescendo-decrescendo (diamond-shaped)	2nd rt i s	Carotids apex	Leaning forward	Diminished or absent A_2, systolic thrill
Aortic dilatation	Systolic	High		Decrescendo	2nd-3rd rt i s	Carotids	Erect	Accentuated A_2
Pulmonic stenosis	Systolic	High	Coarse	Crescendo-decrescendo (diamond shaped)	2nd-3rd lt i s	↓ sternum	Leaning forward	Diminished P_2, no splitting, systolic thrill
Mitral insufficiency	Systolic	High	Harsh to squeaky	Invades 1-2 sounds	Apex	Axilla	Supine	Accentuated P_2, systolic thrill
Hemic and flow mur *	Syst and occ diast	High	Variable		Sternum and apex	Variable	Variable	Dependent on underlying lesion
Tricuspid insufficiency	Systolic	High	Harsh	Louder on inspiration	5th lt i s parasternal	Apex	Erect	
Aortic insufficiency	Diastolic	High	Blowing	Decrescendo	3rd lt i s	Apex	Leaning forward	
Pulmonic insufficiency	Diastolic	High	Blowing	Decrescendo	2nd-3rd lt i s	↓ sternum	Erect	Accentuated P_2
Patent ductus	Systolic and Diastolic	High	Harsh	Systolic accent	1st-2nd lt i s	↑ carotids ↓ sternum	Erect	Accentuated P_2; Continuous thrill
Aortic Pulmonary defect	Systolic and Diastolic	High	Harsh	Systolic accent	3rd lt i s	↑ carotids ↓ sternum	Erect	Accentuated P_2; Continuous thrill
Arteriovenous fistula	Systolic and Diastolic	High	Harsh	Systolic accent	Over site of fistula			Overactive heart; Continuous thrill
I V S D (Roger's)	Systolic	High	Harsh	Even intensity	3rd-4th lt i s	Left lateral		

* Increased velocity and volume of flow (anemia, left to right shunts, hypermetabolic states, etc)

ness of the percussion note occurs with pulmonary consolidation, pleural fluid, pericardial effusion and enlargement of the heart chambers or great vessels. Percussion may also confirm displacement of the cardiac borders to the left as well as to the right and may aid in differentiating lateral displacement from enlargement

Auscultation

In the past two decades renewed interest in heart sounds and their recording as well as improved methods of correlating heart sounds with other cardiac phenomena have explained many auscultatory findings and have elucidated constellations of findings with definitive clinical implications, often recognizable at the bedside Reference is made to Chapter 6 on phonocardiography and Chapters 9 and 10 on cardiovascular dynamics for further discussion of these relationships.

The ear identifies vibrations of certain frequencies and certain intensities as sound. Audible frequencies are from 20 to 20,000 vibrations per second, the slower the frequency the lower the *pitch*, the higher the frequency the higher the pitch. The *quality* of the sound results from the overtones (higher frequency vibrations) *Intensity* refers to the amplitude of the vibration and in clinical usage is synonymous with *loudness*. The ear is progressively less sensitive to sounds with frequencies under 500 per second, which is in the frequency range of most heart sounds, therefore, a low-frequency sound of a certain intensity appears less loud to the ear than a high-frequency sound of the same intensity In addition, the ear exhibits the phenomenon of *masking*, whereby intense sounds render inaudible adjacent, less intense sounds, or high-frequency sounds inaudible adjacent to equally intense, low-frequency sounds.

Sounds generated within the heart or blood vessels are transmitted by surrounding media

to the body surface. Alterations in density of the transmitting media affect the intensity, the quality and the pitch of the sounds. The intensity also diminishes with the square of the distance from the point of origin.

The characteristics which enable the stethoscope to transmit the sound with minimal alterations in intensity, quality and pitch from the body surface to the ear have recently been studied.[7] In general, the ear pieces must be snug, parallel to the long axis of the auditory canal and airtight. The tubing should not exceed 12 inches in length and should be thick-walled with an inner diameter of 1/8 inch The chest piece should be of the bell type with a diameter of about 1 inch and a small internal volume An interchangeable diaphragm of rigid bakelite should be included The bell is used for low-pitched sounds, the diaphragm to accentuate high-pitched sounds and mask low-pitched sounds. In use of the bell the lightest application consistent with an airtight seal of the skin results in greatest audibility of low-pitched sounds. Increasing pressure on the bell tightens the underlying skin causing it to act as a diaphragm, masking low-pitched sound, decreasing the loudness of the sounds and increasing audibility of high-pitched sounds

The technic of cardiac auscultation should follow a pattern involving sequential auscultation of the entire precordium and multiple positioning of the patient. Attention should be focused successively on the first sound, the second sound, extra sounds and the intervals between sounds, noting the occurrence and characteristics of murmurs and adventitious sounds.

Heart Sounds

Descriptions of heart sounds and details of their aberrations are found in Chapter 6 (phonocardiography). The heart sounds vary from the normal in loudness, number, pitch and quality. The first heart sound is significant at the apex, the second sound at the base.

Variations in Intensity of Heart Sounds

1 *Increased intensity of both heart sounds* is usually due to a thin chest, cardiac overactivity or a heart close to the chest wall

2 *Decreased intensity of both heart sounds* may result from noncardiac causes such as a heavy chest wall (obesity), hyperinflation of the lungs (emphysema), the damping effect of fluid (pleural or pericardial) and cardiac causes such as myocardial infarction, myocarditis, myxedema or mechanically restrictive diseases

3 *Variations in the intensity of alternate pairs of heart sounds* is mechanical alternation and may occur early in left ventricular failure or in *paroxysmal tachycardias Its pathogenesis* is related to impaired contractility and relative muscle refractoriness in alternate beats.

4. *Increased intensity of the first heart sound* is significant only at the apex and occurs with shortened A-V conduction from any cause, or with the elevated left atrial pressure of mitral stenosis. With shortened A-V conduction the mechanical ventricular contraction closely follows the mechanical atrial contraction. The widely opened mitral leaflets thereby forcefully close resulting in accentuation of the first sound. In mitral stenosis the loud apical first sound accompanies elevated left atrial pressure delaying mitral valve closure until ventricular systole is powerful and quick.

5 *Increased intensity of the second heart sound* is significant at the pulmonary and *aortic areas and indicates increased proximity* of the underlying vessel (aorta to the right and pulmonary artery to the left in the second interspace) or increased tension in the involved circuit The classic example of the effect of proximity is the change from the louder P_2 of youth to the loud A_2 of adult life associated with the counterclockwise rotation of the heart and great vessels

6 *A decrease in intensity of the first heart sound* occurs at the apex with prolonged A-V conduction It also occurs in mitral insufficiency due to the masking effect of the very loud, adjacent systolic murmur as well as the valve deformity preventing apposition.

7 *Decreased intensity of the second heart sound* is significant only at the base and occurs at the aortic or pulmonic valve area. The audible second sound is produced chiefly by closure of the aortic and pulmonic valves, and stenosis of either tends to reduce or eliminate the sound

of closure over the affected valve area. Similarly, in insufficiency of either valve, the closing sound is reduced in intensity by the valve defect as well as masked by the adjacent early diastolic murmur.

Variations in Number of Heart Sounds

The number of heart sounds may vary by the absence of one sound, by splitting of either sound, or by the development of extra sounds in systole or diastole, of insufficient duration to be termed a murmur Splitting of heart sounds is clinically differentiated from extra heart sounds by the observation that the two components do not exceed the ordinary length of the normal heart sound

Split Heart Sounds

1 *Splitting of the first heart sound* when best heard at or near the base is termed an aortic or pulmonic opening snap or ejection sound dependent on whether it is best heard to the right or left of the sternum It is associated with hypertension or arterial dilatation of the involved circuit, and is due to audible separation of the second (A-V closure) and third (semilunar opening) components of the phonocardiographic vibrations constituting the first heart sound. Apical splitting of the first sound results from audible asynchrony in tricuspid and mitral closure Clinically, it is impossible to differentiate that resulting from bundle-branch block from that occurring normally.

A split first sound must be differentiated from an audible fourth sound, a presystolic gallop or from a systolic click In all these instances the duration of the two components exceeds the normal duration of the first sound.

2. *Splitting of the second heart sound* occurs when a sound of slightly more than normal length is separated by a central inaudible component It is heard over the base and usually is loudest in the second or third left interspace parasternally. The audible second sound is due to closure of the aortic and pulmonic valves. Closure is quite synchronous in expiration, but with inspiration right ventricular systole and, therefore, pulmonary closure are prolonged and cause an audible normal splitting. "Expiratory splitting" is abnormal. In left bundle-branch block, aortic closure is delayed beyond pulmonic closure and becomes more evident in expiration This represents paradoxical splitting In right bundle-branch block, right heart contraction and pulmonic closure are delayed and the splitting becomes wider and louder with inspiration Increased right or left ventricular emptying time may also cause asynchrony in valve closure and splitting of the second sound Confused with splitting of the second sound are third heart sounds and protodiastolic gallop sounds. Both of these are sounds which are loudest just inside the apex rather than at the base.

Extra Heart Sounds

1 *The third heart sound* is here termed an "extra sound" only because it is of low frequency and is usually inaudible under normal circumstances. It represents vibrations set up by rapid ventricular filling in early diastole It is heard with slow heart rates Its presence with a rapid heart gives rise to the protodiastolic gallop rhythm In certain cases of constrictive pericarditis, accentuation of the third sound may occur and is termed the "filling sound."

2 *The fourth heart sound* is presystolic and is due to vibrations set up by atrial contraction. It is heard inside the apex and along the left lower sternal margin as a low-pitched, low-frequency sound in normal individuals. It is frequently heard with increased venous return, atrial enlargement and increased atrial blood flow or blood pressure. In the presence of a rapid rate and gallop cadence, it is termed a presystolic gallop.

3 *An opening mitral snap* is best heard at or just inside the apex and may be transmitted to the base. It is always associated with a loud or booming apical first sound and has a snapping quality It is due to the forceful opening of the leathery stenotic mitral valve under the increased pressure chronically present in the left atrium and is frequently associated with accentuation and splitting of P_2 due to the associated pulmonary hypertension It is differentiated from a split P_2 by its greater intensity near the apex and its constancy in inspiration and expiration When present, it

has considerable diagnostic reliability in mitral stenosis

4. *Gallop rhythm* is a tripling of heart sounds simulating the canter or gallop of a horse It is differentiated into systolic gallops of unknown clinical significance and uncertain explanation, and diastolic gallops usually signifying heart failure, impending or present

5. *Systolic clicks* are high-pitched sounds varying in intensity from beat to beat, usually heard between the apex and sternal margin and usually in midsystole. They are of unknown cause and no clinical significance

Variations in Pitch of Heart Sounds

The pitch of the two heart sounds may be so altered as to become indistinguishable. When this occurs with a rate sufficiently rapid that the systolic and diastolic intervals are approximately equal, the resulting heart sounds resemble the ticking of a clock and are termed a "tic toc" rhythm.

Variations in Quality of Heart Sounds

Through the addition of overtones, musical elements may be added to the heart sounds changing the muffled quality to a tympanitic (tambour) quality or to a snap or click The tympanitic quality occurs particularly in association with the second heart sound, it is located at the base and usually associated with increased intensity of the sound When present over the second right interspace, it suggests hypertension of the systemic circuit with loss of vascular elasticity Its presence at the second left interspace suggests similar changes in the pulmonary circuit.

Heart Murmurs

Heart murmurs are described in detail in Chapter 6. Murmurs may be extravascular or intravascular. The latter may have their origin from eddy currents (turbulence) within the heart or within the blood vessels. They do not, therefore, constitute indubitable evidence of heart disease as does cardiac enlargement Some murmurs are very suggestive of valvular or vascular disease and should arouse suspicion as to the possible presence of cardiovascular disease

Murmurs are due to turbulence of bloo flow An understanding of the factors produ ing turbulence of flow is helpful Important a the velocity of blood flow, the viscosity of th blood, obstruction to flow and reversals of flov Increasing the velocity of flow, decreasing th viscosity of the blood, or combinations o both, with or without obstruction or reversa of flow, may cause turbulence to appear o disappear. Turbulence becomes audible whe vibrations which it sets up in surroundin structures are transmitted to the ear and ar in the frequency ranges which may be audibl to the ear

In searching for and evaluating a murmur the various factors responsible for murmu production and murmur audibility must be considered and altered. One may increase the intensity of a murmur by positioning the patient to approximate the vibrating structure as closely as possible to the chest wall. It is important when searching for the murmur of mitral stenosis to listen at the apex with the patient lying on the left side after exercise has increased the velocity of blood flow A maneuver of value in detecting early aortic insufficiency is to listen for the aortic diastolic murmur with the patient leaning forward and holding the breath after a maximal exhalation. Exercise of the patient will increase the velocity of blood flow, sometimes passing the critical level at which obstruction gives rise to turbulence and thus bringing out a murmur or simply accentuating the degree of turbulence and the intensity of the murmur The Valsalva maneuver may alter flow relationships and cause murmurs to disappear and reappear in characteristic temporal relation to the side of the heart involved Ordinary breathing frequently alters the intensity of murmurs. Likewise, hyperthyroidism, anemia etc may increase velocity of flow sufficiently to produce murmurs which disappear with correction of the underlying state Decreased velocity and increased viscosity may cause murmurs to disappear because of the damping effect on turbulence Thus, the murmur of mitral stenosis may not be heard during heart failure.

In TABLE 1 some of the more commonly heard murmurs are presented with their im-

portant characteristics and associated signs More detailed descriptions of heart murmurs are presented in Chapters 6, 14 and 15.

Other Adventitious Sounds

Pericardial friction rubs are loud, usually sharply localized, scratchy or grating to-and-fro sounds appearing close to the ear and dissociated from the heart sounds They are frequently evanescent and occur in only one rather fixed phase of the respiratory cycle. They occur in rheumatic and collagen diseases, pleuropulmonary infections, cardiac trauma, myocardial infarction, uremia, cachectic states and virus infections. In uremia, they are unassociated with pain. In nonspecific pericarditis, they may persist for weeks or months.

Pericardial knocks are loud superficial snapping sounds associated with pneumothorax or dilatation of the stomach.

The mediastinal crunches of mediastinal emphysema are continuous grinding sounds produced by the heart beating against the air-containing mediastinal tissue

Venous hums are common in children They are also common with increased blood flow such as occurs in thyrotoxicosis, anemia and post-exertional states They occur most commonly above the clavicles but may at times be heard over the base of the heart as a low-pitched continuous murmur with diastolic accentuation. Compression of the internal jugular vein on the side of the hum causes its disappearance, because it is due to the turbulence of blood flow in the large veins of the neck and thorax. The upright position accentuates the hum, the horizontal position decreases the hum (and the rate of flow down from the head).

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Electrocardiography and Vectorcardiography

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WHEN living cells are in the resting state, a difference of potential exists across the cell membrane, the inside being negative with respect to the outside A record of this potential difference cannot be made by external leads due to the high impedance of the membrane. This means that all points in a homogeneous conducting medium surrounding a resting cell have the same potential and no current flows between any two of them.

The difference of potential across the membrane during the resting state, called "membrane resting potential" (M R.P), has been measured in several living cells by inserting one microelectrode inside the cell and another on the outer surface of the membrane Resting potentials of cardiac cells show variable magnitudes from 50 to 110 millivolts according to different authors. These differences are not striking and may simply depend on the size of the myocardial fiber

The concentration ratios of potassium and chloride ions partially account for the transmembrane resting potential, but other ions must also be taken into consideration There exist within the cell both positively charged potassium ions and large negatively charged ions (proteins, chloride, phosphate and amino acids) In addition, the sodium ion concentration is larger outside than inside the cell An "active sodium pump" mechanism has been considered as the process responsible for the extrusion of intracellular sodium.[20]

When a resting excitable cell is stimulated, important changes take place:

1. Changes in the electrical properties of the membrane. The conductance of the membrane increases up to 200 times that of its resting value. As an immediate result the electromotive force across the membrane diminishes.

2. The change in permeability of the membrane permits a free flow of ions, sodium and potassium currents moving down their own electrochemical gradients. Since the concentration of the positively charged sodium ions is more than ten times greater outside than inside the cell, the gradient permits an important volume of sodium ions to enter the cell. The consequence of this first ion current is depolarization of the membrane; later on, the membrane potential reverses its sign. Potassium current starts flowing shortly after the beginning of sodium mobilization Since the concentration of potassium is greater inside than outside the cell, the flow of this ion current is directed from inside out [16] When it exceeds the sodium current, it starts the repolarization of the membrane (FIG. 1)

3. As a consequence of the ionic currents, the membrane potential rapidly falls to zero (depolarization) and then reverses itself, so that the inside of the cell becomes positive with respect to the outside (reversal of polarization, or overshooting). This reversal of potential (FIG. 1) is a very fleeting phenomenon, for it is rapidly supplanted by the changes that take place during the recovery process. As mentioned above, the reversed current is, according to Cole,[5] a short burst of sodium ions crossing, whereas the later current is due to a steady flow of potassium ions

The simplest tracing which results from all these events is called the monophasic action potential (FIG 1) or membrane action potential (M A P), or transmembrane action potential This kind of tracing can be obtained by inserting an exploring microelectrode into the cell and placing another electrode either far or near in the surrounding conducting medium. Similar records may be obtained by injuring one end of the cell, pairing one electrode on that end and the other one on an uninjured portion of the same tissue.

In the monophasic action potential one can

distinguish the following portions (FIG 1): The upstroke, which corresponds to the depolarization of the cell; the vertex, or reversal polarization spike, which is inscribed at the moment of reverse polarization; and the slow descending portion, which is related to the recovery or repolarization phenomenom This means the return of the cardiac cell to the resting state is a prolonged process. It commences fairly rapidly, flattens out to a plateau of long duration and then gradually approaches the resting level These three phases are clearly seen in FIGURE 1.

Some different monophasic action potentials exist in other tissues, but these are not within the scope of this paper

EXPERIMENTS ON VOLUME CONDUCTORS AND THE DIPOLE THEORY

With isolated tissues, two electrodes are placed directly on the tissue concerned It is implied that the currents generated by the activation wave, as well as those of recovery, can be transmitted to the electrodes only via the thin film or fluid lying on the outside of the cell tissue This is the so-called axial current.[18]

In excited tissues immersed in a conducting medium, current flows through the medium from points in inactivated portions to other points situated in the activated portions. If the electrode is placed in direct contact with the tissue, the magnitude of this current is relatively great and the recorded voltages correspondingly large, the current magnitude diminishes rapidly as the electrode is moved away from the tissue or from the heart

The point at which the greatest amount of current flows from the muscular tissue into the conducting medium has the greatest positive potential and may be called the "source" or place of greatest positivity of the medium. It corresponds to the front of the activation wave. The point at which the greatest amount of current flows from the conducting medium into the muscular tissue is the one with the greatest negative potential, this point may be called the "sink" It corresponds to the tail of the activation wave.

Thus, there is created in the medium, but

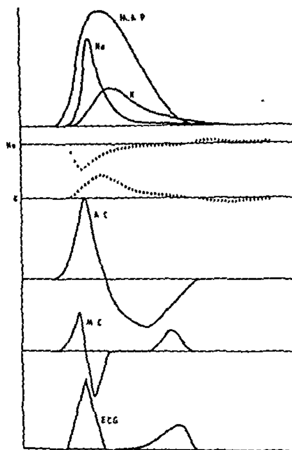


FIG 1 —M A P, monophasic action potential; A C, axial current; M C, membrane current The arrows pointing downward mean that the ion is entering the cell, while the arrows pointing upward mean that the ion is leaving the cell.

intimately related with the muscular fiber, a dipole which in turn sets up an electric field throughout the medium which surrounds the muscle. This dipole in effect moves through the medium as the activation process proceeds from one end of the fiber to the other

THE ACTIVATION WAVE CONSIDERED AS A DIPOLE

As far as the medium surrounding the excitable tissue is concerned, the activation wave may be considered as a crest preceded by a positive pole (source) and followed by a negative pole (sink). We are indebted to Craib[6] and to Wilson[21] for the concepts outlined above. The activation process may be represented graphically as a dipole which progresses along the outer aspect of the cell membrane.

Let us now turn our attention to the recording of these electrical events. One may take, for example, a small portion of contractile muscle (Fig 2) immersed in an extensive conducting medium. One electrode is placed sufficiently far away in the conducting medium so that the influence of the electrical field produced by muscular activity is negligible, this becomes the indifferent electrode The exploring electrode is connected to the positive pole of a recording galvanometer, and the indifferent electrode to the negative pole The exploring electrode is then placed *serially at points A, B* and *C* of Figure 2

When, under these conditions, the muscle is stimulated at its left end, as by an electric shock, the curves recorded at the three respective points are quite variable At *A*, the curve is entirely negative At *B*, it is diphasic (of the plus-minus type) At *C*, it is wholly positive (Note that we are speaking only of the activation process, not recovery) If now we relate these curves with the progress of the dipoles of activation as outlined above, we see that the excitation wave, conceived as a dipole, *with a positive pole (source) followed by a* negative pole (sink), produces a positive potential variation as it approaches a given point (Fig. 2, *C*) and a negative potential variation as it moves away from that point (Fig 2, *A*). Figure 2, *B* can be readily analyzed, for during the first half of its inscription the activation wave is moving toward that point (hence an upward deflection denoting a positive potential variation), and during the second half the wave was moving away from that point (hence the downward deflection of a negative potential variation).

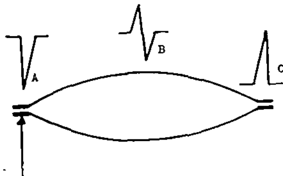


Figure 2

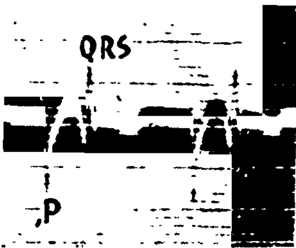


Fig. 3 – Unipolar intracavitary tracing obtained near the sinus node Note the negative P wave with greater voltage than the QRS complex

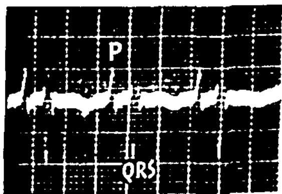


Fig 4 —Unipolar intracavitary tracing obtained at the lower level of the right atrium Note the positive P wave

These ideas are in agreement with some electrocardiographic findings In studying the intracavitary potentials of the human heart, we have been able to obtain negative P waves (Fig 3) when the exploring electrode was placed at the level of the superior vena cava near the sinus node. When the exploring electrode was placed at the inferior vena cava or the lowest portion of the atrium, the P wave was entirely positive or almost so (Fig. 4). Midway between the two points, the curve was plus-minus diphasic (Fig. 5). In a case with interatrial septal defect, we have obtained intracavitary tracings characteristic of the left atrium, namely, almost unmixed positivity.

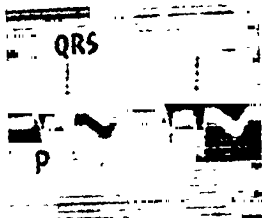


FIG 5—Unipolar intracavitary tracing recorded near the middle of the right atrium Note the diphasic P wave, first positive and then negative

Curve of the Activation Wave

In the left ventricular cavity of the dog's heart, Wilson and associates[21] found that the curve representing ventricular activation (QRS) is entirely negative In the right ventricular cavity, there was a very small initial positive deflection followed by a deep negative deflection. We have obtained similar tracings in the right ventricle in man in our studies of intracavitary potentials (FIG 6). In the light of the above concepts, the curve of negativity obtained inside the left ventricular cavity implies that the activation wave is spreading entirely from endocardium to epicardium, this is in keeping with Lewis' findings of many years ago[8] Similarly the initial small positive deflection of curves obtained in the right ventricular cavity is explained by the very early activation of some portion of the left septal surface, moving from left to right, the remainder of the curve, negative in its entirety, implies that the activation wave is moving from endocardium to epicardium in the wall of the two ventricles

The curve of the activation wave is summarized graphically in FIGURE 7 As long as the dipole of activation is at a considerable distance from the electrode, the field of the dipole has no appreciable influence on the electrode, and the base line of the tracing remains isoelectric (FIG. 7, *1*) As the dipole approaches the electrode (the positive pole being in the lead), the latter finds itself in the electric field of the dipole; its positive charge begins to have some influence on the electrode, and a positive deflection begins to be inscribed in the curve (FIG. 7, *2*). When the positive pole of the excitation wave is under or nearest to the electrode, the greatest positivity is registered (FIG. 7, *3*) When the electrode is midway between the positive and negative poles (FIG. 7, *4*), its potential is zero and the tracing returns to the isoelectric line. When the negative pole is under the electrode or very close to it, the greatest negativity appears in the record (FIG. 7, *5*). When the activation wave moves away from the electrode, the negativity decreases (FIG. 7, *6*) until the line becomes isoelectric again (Fig. 7, 7). By convention in electrocardiography, the positive deflection just de-

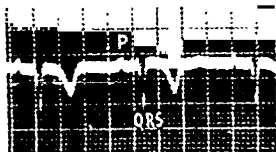


FIG 6—Unipolar tracing obtained in the right ventricular cavity The ventricular complex is of the RS type

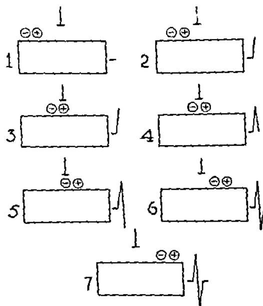


FIGURE 7

scribed is called the R wave, the negative deflection is the S wave because it follows the R wave, a negative deflection preceding R is called Q.

One can now understand that when a positive deflection is seen in the electrocardiogram, it infers that *the activation wave is moving* toward the electrode concerned, a negative deflection *indicates that the activation wave* is moving away from the electrode.

Curve of the Recovery Process

As has been described,[16] the recovery process may be envisioned as involving a wavelike passage of a dipole along the surface of the cell membrane, with the negative pole preceding the positive pole, in other words, the opposite of the conditions which obtain as the activation wave spreads along the cell membrane Theoretically, therefore, curves exactly opposite of those shown at *A*, *B* and *C* of FIGURE 2 should be expected as records of the recovery process *Actually, however, tracings recorded* during recovery (called T wave) differ rather markedly from those belonging to the rapid complexes (i e , those of activation), for the following reasons:

1. The deflection obtained during recovery is of longer duration and has a rounded shape, which is due simply to the fact that the recovery process is slower than the activation process.

2. Only the positive part of the T wave may be seen Macleod has shown that the repolarization (recovery) process in some regions of the heart starts before the end of the depolarization (activation) process *in* other regions. For this reason, the first part of the T wave may be superimposed *on the last part* of the S wave, a summation of complexes occurs *Consequently, the first part of the* T wave may be masked by the last part of the S wave. Bayley,[2] *on the other hand,* has been able to register the negative and the positive deflections of the *recovery* process that would be expected theoretically from the preceding diphasic *(plus-minus)* rapid complex (FIG. 8).

3 The regression curve is easily modified by a *number* of influences These may not affect depolarization and yet have a profound effect

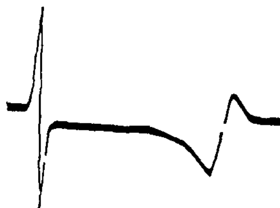


FIGURE 8

on the repolarization (recovery) process, so that the direction and sequence of the latter may be quite different from those of depolarization.

THE EINTHOVEN HYPOTHESIS

So far, the activation wave can be considered as a dipole The experiments and theoretical discussions *of Craib*[6] *and Wilson*[21] *reinforce* this viewpoint It is another step, however, to consider all the electrical forces of the heart as a dipole [7] In other words, at any given moment in the cardiac cycle the electromotive forces created by the heart are mathematically equivalent to a single dipole This dipole, according to Einthoven,[7] lies in the center of an imaginary equilateral triangle The apices of this bidimensional geometric figure (triangle) are located at the acromial processes of the two scapulae and at the pubic region. The sides of the triangle *correspond to the three standard* leads of the electrocardiogram The medium *in which the triangle lies was considered* by Einthoven to be a homogeneous sheet of conducting *material. The triangle is thus seen to* lie in the frontal plane of the body; but its location along the anteroposterior plane of the body, i e , its depth in the chest, is unknown. This latter limitation is of no importance in ordinary electrocardiography but is of considerable significance in spatial vectorcardiography

In comparison to the relatively great size of the triangle, the two charges of the dipole are placed so close together that the triangle itself may be considered as being infinitely large.

Another way of visualizing this postulate is to imagine the dipole as lying in the center of a very large sphere, on the surface of which are located the apices of the equilateral triangle.[18]

Einthoven's justification for considering the heart as a dipole situated in the center of this large equilateral triangle is based on a well known theorem which refers to a complex of charges distributed in a dielectric enclosed in a sphere of a minimum adequate radius.[19] The voltage produced by the charges can be registered at a point P placed outside the sphere. The formula expressing this potential is developed in an infinite series of harmonics.

Let us suppose, for example, that the heart is enclosed in a very large sphere. During the process of activation, there are some points where current leaves the heart to be distributed through the surrounding tissues, as well as other points where this current returns to the heart. (This is true for each one of the muscular fibers of the heart.) We can therefore suppose the presence of a "source" or positive region for each point where the current leaves, and a "sink" or negative region in each place where the current returns. The potential for equal charges of opposite sign can be calculated mathematically and a formula developed in an infinite series of harmonics. The first term of the series is zero, because it corresponds to the sum of all the charges and these have opposite signs. The second term represents the potential of a dipole, and in the corresponding formula it is $\cos \theta/r^2$ (where r represents a line drawn from point P to the center of the dipole, and θ is the angle formed by this line and the axis of the dipole). The third term corresponds to the potential of a quadripole, represented mathematically by the formula $\cos^2 \theta/r^3$. The fourth term would correspond to the potential of an octopole, and so on.

From an examination of these various terms, it is apparent that if the point P is sufficiently distant from the center of the sphere, the value of r will become so large that all the terms of the series tend to disappear, with the result that the only term remaining is that of the dipole. It is evident, therefore, that Einthoven's conception of considering the heart as a dipole in the center of a very large triangle made of homogeneous material, was entirely valid.

The orientation of the dipole depends on those areas where the largest amount of current leaves or enters the heart during activation.[17] Since the current magnitude varies considerably during the cardiac electrical cycle, the orientation of the different dipoles also varies in the same proportion.

The vector which goes from the negative to the positive charge of the dipole is called the "instantaneous electrical axis." The magnitude of this vector depends on the value of the charges and the distance which separates them.

We must keep in mind that the vector representing the instantaneous electrical axis of the heart is the resultant of many vectors, since there are many areas of electrical activity in the heart, each one giving rise to its own individual vector: the vectorial summation constitutes the instantaneous electrical axis.

Vectorcardiography and Stereo-vectorcardiography

The concepts explained above indicate that during the activation process, the duration and magnitude of the activation vary from moment to moment in the cardiac cycle, and the summation of the cardiac vectors describes a continuous curve called "vectorcardiogram." This term means that the curve is a vectorial function of time.

The vectorcardiographic curve is actually located *three-dimensionally* in space, but for graphic presentation it can be projected to various planes: frontal, horizontal and sagittal. We therefore distinguish between a spatial vectorcardiogram (which of necessity involves a three-dimensional reference frame) and the frontal, horizontal and sagittal vectorcardiograms, which are the projection of the spatial vectorcardiogram on the corresponding planes. The different methods for the registration of vectorcardiograms are not discussed in the present communication.

The Normal Activation of the Human Heart

Recent investigations on the sequence of ventricular activation have shown it to be a

very complex phenomenon.[9-12] For purposes of simplification, Peñaloza and Tranchesi[14] have represented the process of normal activation by three main vectors:

1. The first vector ("septal vector") corresponds to the activation of the middle third of the interventricular septum. The origin of this vector can be localized at the middle portion of the left septal surface and its terminus at the base of the anterior papillary muscle on the right septal surface. In space, the vector is directed forward and to the right, sometimes upward, other times downward, depending on the rotation of the heart.

This vector (Fig. 9, *1*) accounts for the small q wave usually seen in the left precordial leads (V_5 and V_6) and for the small r wave in the right precordial leads (V_1 and V_2). This activation also explains satisfactorily the first portion of the vectorcardiogram (Q loop; Fig. 10, *1*).

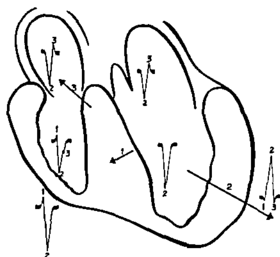


Fig. 9.—Unipolar normal patterns related to the three main vectors of normal activation.



Fig. 10.—Normal vectorcardiograms in the frontal (*above*) and horizontal (*below*) planes. The numbers represent the time sequence of the three main vectors of activation of the QRS loop.

2. The second vector (Figs. 9, *2* and 10, *2*) corresponds to the activation of the free left ventricular wall (vector of the left ventricle). We know that the free right ventricular wall is depolarized at the same time, but the magnitudes of the electrical forces produced in this ventricle are very small in comparison to those produced by the free left ventricular wall. This is the reason why we do not consider the electrical events produced in the major part of the free right ventricular wall.

The second vector is directed to the left and toward the back, sometimes upward, other times downward, depending on the position of the heart. The reason for this orientation is that the vector travels from the center of the free left ventricular cavity to the centroid of the mass of the free left ventricular wall; in other words, it moves perpendicularly from endocardium to epicardium, in a region equidistant from both anterior and posterior interventricular grooves. The spatial orientation of this vector explains the tall R wave in V_{5-6} and the deep S waves in V_{1-2}. This vector also explains the major development of the spatial vectorcardiographic curve (Figs. 9 and 10). Normally, the second vector coincides with, or is very near, the general direction of ventricular activation (SÂQRS).

3. The third vector is related to the activation of the basal portions of the heart. The basal regions of the free right and left ventricular walls and basal portions of the interventricular septum which belong mainly to the right septal mass and include the crista supraventricularis.

The third vector (Figs. 9, *3* and 10, *3*) is oriented toward the right, generally upward and slightly backward. It accounts for the terminal negativity (s waves) in V_{5-6} and the terminal positivity (r or r′) frequently recorded in the unipolar lead of the right arm (VR). It also explains the terminal portion (S loop) of the vectorcardiographic curve.

These three main vectors of ventricular ac-

tivation reasonably explain the main deflections of the direct records obtained at the epicardial and endocardial surfaces of the atria and ventricles.

Clinical Usefulness of the Electrocardiogram

The electrocardiogram is valuable in the following clinical conditions:

1 Ventricular and atrial hypertrophy and dilatation

2. Myocardial infarction and other manifestations of coronary disease ischemia, subendocardial injury etc.

3 Arrhythmias ventricular, atrial and nodal tachycardias, atrial flutter and fibrillation; premature beats etc

4 Disturbances of intraventricular conduction Right and left incomplete or complete bundle-branch

cardiogram gives most information.

6 Pericarditis regardless of the etiology.

7 Effect of some cardiac drugs, especially digitalis and quinidine

8 Electrolyte disturbances such as hypopotassemia and hyperpotassemia, hypocalcemia and hypercalcemia or combinations of these

9 Systolic and diastolic overloading These will be discussed in greater detail.

in

electrocardiography (contrary to general opinion) in the diagnosis and hemodynamic situation of the most important cyanotic and acyanotic congenital malformations of the heart and great vessels.

Since it is impossible in the present chapter to discuss all these topics, we have chosen a few problems in which we have been active in experimental and clinical investigation

Right and Left Bundle-Branch Block

Right bundle-branch block (R B B.B.). The unipolar patterns of the electrocardiogram and the spatial orientation of the vectorcardiographic curve are satisfactorily explained by the sequence of ventricular activation in this condition.

In R B.B B four main vectors of activation should be considered:

1. A septal vector which is the same as that described for normal activation, since the left septal surface is depolarized at its normal time due to the integrity of the left bundle branch, this activation determines the inscription of the first small positivity in V_1 and V_2, the small q wave in V_5 and V_6 (Fig. 11, *1*) and the first portion of the vectorcardiographic curve (Fig 12).

2. A vector at the free left ventricular wall. Although this is a normal vector or, in other words, although there is a normal activation of the free ventricular wall, the resultant electrical forces are counterbalanced by the third vector which will be described next. The orientation of the electrical forces produced by the activation of the free left ventricular wall is toward the left, back and generally

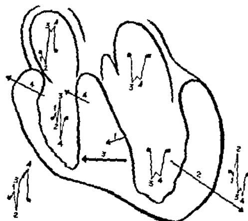


Fig 11.—Unipolar patterns in R B B B ; the four main vectors of activation in this type of block are represented

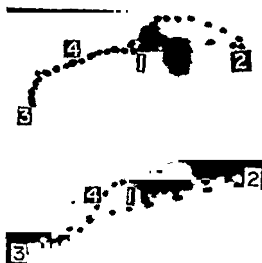


Fig. 12 —Vectorcardiograms in the frontal (*above*) and in the horizontal (*below*) planes in a case of R B B B The numbers represent the time sequence of the four main vectors of activation of the QRS loop.

downward (Fig 11, *2*) These forces explain satisfactorily the S wave of V_1 and V_2 and the R wave (with lower voltage than in normal activation) in the left *precordial leads, V_5 and V_6. They also explain the* orientation of the vectorcardiographic curve to the left and toward the back (Fig 12)

3 A new vector is located at the lower portion of the interventricular septum and is mainly due to bridging of the activation wave from the left to the right septal mass and from the "interseptal barrier" to *the endocardium of the right septal surface* This vector (Fig 11, *3*) is the most important one in R B B B and it explains the upstroke and the initial slurring on the rising limb of the R′ in the right precordial leads, and the descending limb of R and the initial notching of the S wave in V_5 and V_6. It also explains the spatial sense of the vectorcardiographic curve to *the front, toward the right and downward,* as well as the notching recorded during the counterclockwise rotation of this part of the loop (Fig 12)

4 The fourth vector is related to the activation of the basal portions of the right ventricle, which includes the free right ventricular wall and the high right septal mass and crista supraventricularis The second peak of the R′ in V_1 and V_2 and the end portion of the S wave in V_5 and V_6 depend on this fourth vector (Fig 11, *4*) The terminal portions of the *vectorcardiographic loop are also dependent on the* same electrical forces (Fig 12)

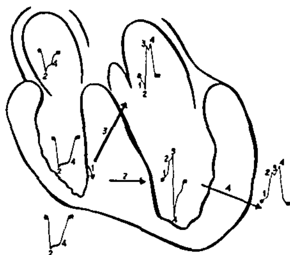


Fig 13 —Unipolar patterns in L B B B , the four main vectors of activation in this type of block are represented

Left bundle-branch block (L B.B B). The sequence of ventricular activation in L B B.B. may also be represented by four main vectors:

1 A vector which corresponds to the *activation* of the middle portions of the right septal mass and, probably, to the bridging of the activation wave from the right septal mass to the left septal mass This activation determines the inscription of a small positive deflection in V_5 and V_6 (Fig 13, *1*) The first portion of the vectorcardiographic curve is oriented toward *the front, down and leftward (Fig 14)*

2 The second vector represents the activation of the left septal mass in the lower portion of its middle third, from the "interseptal barrier" to the lower endocardial surface near the papillary muscle This vector is oriented toward the left, back and downward It explains the upstroke of the R wave in V_5 *and V_6 (Fig 13, 2) and the downstroke of the* S wave in the right precordial leads (V_1 through V_4) In the vectorcardiographic curve these forces (Fig 14, *2*) are represented by the first part of the R loop oriented toward the back and to the left, sometimes upward and other times downward

3 The third vector is also a septal vector due to the activation of the left septal mass in its middle and upper thirds, electrical forces which are oriented toward the left, up and backward The latest part of the left septal mass that becomes depolarized cor*responds in this conduction disturbance to the ante*rior basal portion of this mass We have shown in our experiments that this activation is unusually slow as the front of the activation wave approaches the endocardium of the left septal surface This slow type

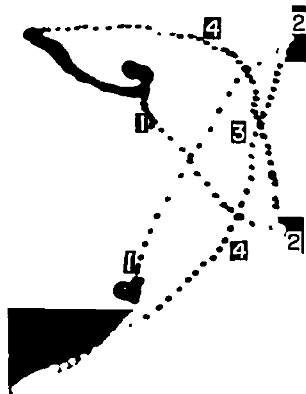


Fig 14 —Vectorcardiograms in the frontal (*above*) and in the horizontal (*below*) planes in a case of L B B B The numbers represent the time sequence of the four main vectors of activation in the QRS loop.

[illegible]

cardiographic loop during the distant portion which is inscribed in a clockwise manner on the horizontal plane (Fig. 14, 3).

4. The fourth and last vector corresponds to the activation of the free left ventricular wall, also oriented toward the back and left, sometimes upward, other times downward (Figs 13, 4 and 14, 4) This vector determines the second peak of the R wave in V_5 and V_6 and the final portions of the S wave in V_1 and V_2 and of the vectorcardiographic loop

Electrolyte Disturbances and their Clinical Significance

Table 1 summarizes the main electrocardiographic findings in electrolyte changes and the main clinical possibilities in which they appear.

Systolic and Diastolic Overloading of the Heart

Cabrera and Monroy[3, 4] described the main changes in the electrocardiogram resulting from systolic and diastolic ventricular overloading. They presented electrocardiographic evidence of a different behavior of the heart according to the type of hemodynamic overloading In primary diastolic overloading, Starling's mechansim is probably the compensatory mediator, while in systolic overloading, Fenn's mechanism explains satisfactorily the cardiac adaptation and the electrocardiographic changes derived.

Later investigation done by Peñaloza and co-workers[13] proved that the electrocardiographic changes could not only be related to the hemodynamic condition but to anatomic and positional changes due to such hemodynamic changes For this reason, we prefer to use the term right ventricular hypertrophy or dilatation with systolic or diastolic overloading of the right ventricle, and similar terminology for the left ventricle

Right ventricular hypertrophy with systolic overloading of the right ventricle. The main electrocardiographic feature of this condition is a tall R wave in right precordial leads V_1 and V_2.

The complexes may be any one of the following types Rs, qR, qRs, rR' and R with or without an initial slurring of the upstroke (Fig 15) The T wave may be positive or negative depending on the degree of the ventricular pressure and on the type of cardiac disease For example, in trilogy of Fallot, in patent ductus and in essential pulmonary hypertension, the T wave is usually negative and sometimes shows the pattern of myocardial ischemia, in ventricular septal defect, in tetralogy of Fallot and in transposition of the great vessels, the T wave may remain positive even if the intracavitary pressure in the right ventricle is high (systolic overloading). Thus, the congenital heart lesions and hemodynamic conditions which result in the right ventricular hypertrophy cannot be differentiated electrocardiographically.

The possibility of mistakes in diagnosing right ventricular hypertrophy with systolic overloading in the presence of tall R waves in the right precordial leads V_1 and V_2 is unlikely. Doubt exists when the patient is less than 3 years old, and in those cases a careful study of the electrocardiogram may help; in infants it is difficult to differentiate between a normal electrocardiogram and one suggestive of right ventricular hypertrophy

Recently Sodi-Pallares and associates[14] have pointed out the main possibilities among congenital heart diseases, when there is right ventricular hypertrophy with systolic overloading

The 10 main possibilities among congenital heart diseases in the presence of tall R waves in V_1 and V_2 are:

1 Essential pulmonary hypertension
2 Patent ductus arteriosus with pulmonary hypertension
3 Ventricular septal defect with pulmonary hypertension
4 Atrial septal defect with pulmonary hypertension
5 Pure pulmonary stenosis
6 Eisenmenger complex
7 Complicated pulmonary stenosis (trilogy, tetralogy and pentalogy of Fallot)
8 Atrioventricularis communis
9 Common trunk
10 Transposition of the great vessels.

We must keep in mind that other diseases than congenital cardiac ones may also give the same electrocardiographic pattern, due to the presence of right ventricular hypertrophy. These are:

1 Mitral disease with significant pulmonary hypertension
2 Chronic cor pulmonale with significant pulmonary hypertension.
3 Fibrocystic disease of the pancreas (mucoviscidosis), which often is confused with congenital heart disease

Right ventricular hypertrophy or dilatation with diastolic overloading of the right ventricle (D.O.R.V.) Cabrera and Monroy[3, 4] emphasized that in some diseases with diastolic overloading of the right ventricle incomplete or

TABLE 1.—*Effect of Electrolyte Imbalances on the Electrocardiogram*

ectrolyte nbalance	P wave: Duration	P wave: Voltage	P-R Interval	QRS: Duration	QRS: Voltage	QRS: Morphology	S-T: Duration	S-T: Displacement	T wave: Duration	T wave: Morphology	Voltage of U wave	Q T	Q U	Fusion of T + U	Clinical
iatremia deficit)				Aug-mented	Aug-mented			Opposite to QRS		Opposite to QRS		Diminished			Low sodium diet Diuretic abuse, Addison's disease
iatremia deficit)	THERE IS NO ACTIVATION														Experimental
:natremia				Dimin-ished	Dimin-ished							Augmented			Hypertonic NaCl solutions
potassemia (3 5 mEq /l) potassemia (2 5 mEq /l) potassemia (2 /l)	Augmented	Aug-mented	Negative displace-ment		Aug-mented		Diminished or increased	Negative Negative Negative or positive	Augmented Augmented Augmented	Low and rounded Isoelectric or plus minus Negative or positive with straight rising limb	Augmented >T Aug-mented some times bifid	Augmented Augmented Diminished	Augmented Augmented Augmented	Yes Yes	Nutritional deficiences, profuse diuresis, diabetes chronic nephritis nephrosis diarrheas, fistulae, artificial kidney, excess of corticosteroids, Cushing, aldosteronism hepatitis, (treatment with Para amino-salicylic Acid postoperative alkalosis, insulin, familial periodic paralysis meningitis, encephalitis encephalic injuries, rapid injections of glucose
rpotassemia (5 mEq /l) rpotassemia (8 0 mEq /l)	Augmented	Diminution or disap-pearance	Incomplete A V block Complete A-V block	Aug-mented (S) >0 12 sec	Diminished Diminished	Often incomplete R B B B Often complete R B B B with wide S wave		Slightly positive or negative Positive or negative	Diminished Diminished	Tall and peaked Makes positive the infantile T in V1 2	Diminished	Normal		Yes	Acute nephritis, low nephrosis nephrosclerosis, urinary obstruction, traumatic shock hemolysis, diabetic acidosis before treatment, adrenocortical insufficiency
ocalcemia							Augmented straight		Diminished	Peaked or negative in precordials		Augmented			Sprue, chronic nephritis, nephrosis hypoparathyroidism, huge transfusions with citrated blood, alkalosis, sodium versenate
ocalcemia with opotassemia							Augmented straight					Augmented		Yes	Sprue, severe diarrheas, fistulae
ocalcemia with erpotassemia				QRS changes of hyperpotassemia are accentuated			Augmented straight		Diminished	Tall and peaked		Augmented			Hypoparathyroidism
ercalcemia percalcemia th hypopotasse a							Dimin-ished or absent Dimin-ished	Diminished	Diminished or normal Augmented	Starts from QRS low voltage Negative and deep	Augmented	Augmented			Hyperparathyroidism, treatment with vitamin D, great bone destructions Hyperparathyroidism, tumors of the hypophysis
dosis		Augmented	Aug-mented	Aug-mented						Tall and peaked					Hyperpotassemia? Low intracellular potassium? Diabetes, uremia
abolic alkalosis								Negative		Diphasic				Yes	Hypopotassemia, treatment with alkalis, aldosteronism; Cushing s
piratory Alkalo								Negative (?)		Flat		Normal			Hyperventilation encephalitis, meningitis, treatment with salicylic acid

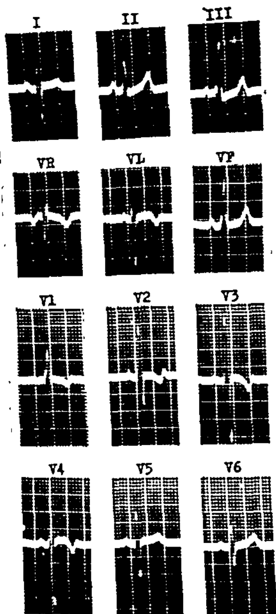


Fig 15 —Tracing suggestive of right ventricular hypertrophy with systolic overloading of the right ventricle

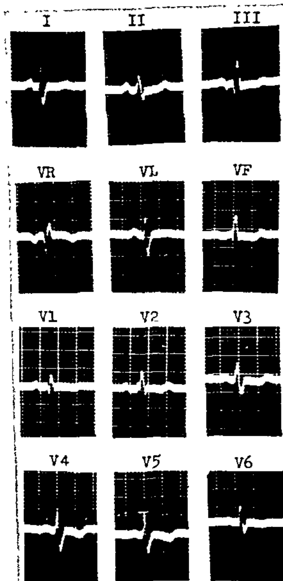


Fig 16 —Incomplete R B B B. The electrical activity of the right ventricle extends over to V_4 and V_5 suggesting right ventricular hypertrophy or dilatation with diastolic overloading of the right ventricle

complete R.B B.B is a common electrocardiographic finding (Fig 16). For example, in some congenital heart diseases in which the right ventricle receives more blood during diastole than the left ventricle, incomplete or complete R B B B is a common finding

Atrial septal defect, anomalous pulmonary veins, congenital pulmonic valvular insufficiency and ventricular septal defect without pulmonary hypertension, all are examples of right ventricular hypertrophy with diastolic overloading of the right ventricle; in all these, incomplete or complete right bundle-branch block may or may not be present. These observations lead to two conclusions

1. In many cases with diastolic overloading of the right ventricle, incomplete or complete right bundle-branch block is present

2 In a number of cases with diastolic overloading

TABLE 1 —*Effect of Electrolyte Imbalances on the Electrocardiogram*

...lyte ...nce	P wave Duration	P wave Voltage	P-R Interval	QRS Duration	QRS Voltage	QRS Morphology	S T Duration	S T Displacement	T wave Duration	T wave Morphology	Voltage of U wave	Q T	Q U	Fusion of T + U	Clinical
...nia ...nt)				Augmented	Augmented			Opposite to QRS		Opposite to QRS		Diminished			Low sodium diet Diuretics abuse, Addison's disease
...mia ...nt)	THERE IS NO ACTIVATION														Experimental
...emia				Diminished	Diminished							Augmented			Hypertonic NaCl solutions
...semia (3 ...q/l) ...semia (2 ...q/l) ...semia (2	Augmented	Augmented	Negative displacement		Augmented		Diminished or increased	Negative Negative Negative or positive	Augmented Augmented Augmented	Low and rounded Isoelectric or plus minus Negative or positive with straight rising limb	Augmented >T Augmented sometimes bifid	Augmented Augmented Diminished	Augmented Augmented Augmented	Yes Yes	Nutritional deficiences, profuse diuresis, diabetes, chronic nephritis, nephrosis, diarrheas, fistulae, artificial kidney, excess of corticosteroids, Cushing, aldosteronism, hepatitis, (treatment with Para amino-salicylic Acid) postoperative alkalosis, insulin, familial periodic paralysis, meningitis, encephalitis, encephalic injuries, rapid injections of glucose
...assemia (5 ...l/l) ...assemia (8 ...q/l)	Augmented	Diminution or disappearance	Incomplete A-V block Complete A V block	Augmented (S) >0 12 sec	Diminished Diminished	Often incomplete R B B B Often complete R B B B with wide S wave		Slightly positive or negative Positive or negative	Diminished Diminished	Tall and peaked Makes positive the infantile T in V1 2	Diminished	Normal		Yes	Acute nephritis, low nephrosis, nephrosclerosis, urinary obstruction, traumatic shock, hemolysis, diabetic acidosis before treatment, adrenocortical insufficiency
...emia							Augmented straight		Diminished	Peaked or negative in precordials		Augmented			Sprue, chronic nephritis, nephrosis, hypoparathyroidism; huge transfusions with citrated blood; alkalosis, sodium versenate
...emia with ...assemia							Augmented straight					Augmented		Yes	Sprue, severe diarrheas, fistulae
...emia with ...tassemia				QRS changes of hyperpotassemia are accentuated			Augmented straight		Diminished	Tall and peaked		Augmented			Hypoparathyroidism
...cemia							Diminished or absent		Diminished or normal	Starts from QRS low voltage		Augmented			Hyperparathyroidism, treatment with vitamin D, great bone destructions
...cemia ...popotasse							Diminished	Diminished	Augmented	Negative and deep	Augmented				Hyperparathyroidism; tumors of the hypophysis
		Augmented	Augmented	Augmented						Tall and peaked					Hyperpotassemia? Low intracellular potassium? Diabetes, uremia
... alkalosis								Negative		Diphasic				Yes	Hypopotassemia, treatment with alkalis; aldosteronism; Cushing's
...ry Alkalo								Negative (?)		Flat		Normal			Hyperventilation encephalitis, meningitis, treatment with salicylic acid

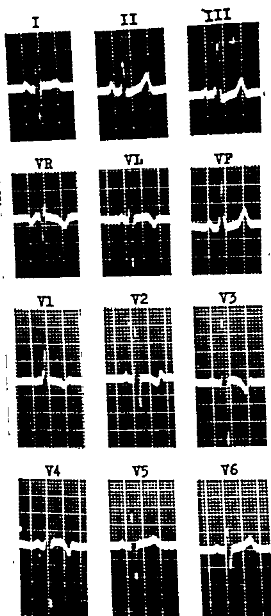


FIG 15 —Tracing suggestive of right ventricular hypertrophy with systolic overloading of the right ventricle

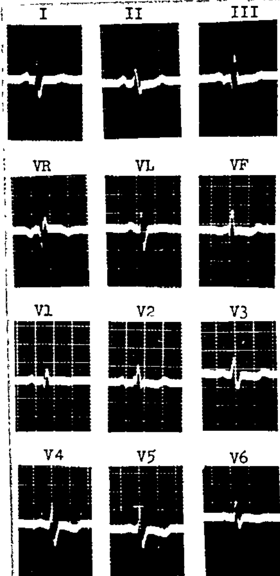


FIG. 16 —Incomplete R B B B The electrical activity of the right ventricle extends over to V_4 and V_5 suggesting right ventricular hypertrophy or dilatation with diastolic overloading of the right ventricle

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Atrial septal defect, anomalous pulmonary veins, congenital pulmonic valvular insufficiency and ventricular septal defect without pulmonary hypertension, all are examples of right ventricular hypertrophy with diastolic overloading of the right ventricle; in all these, incomplete or complete right bundle-branch block may or may not be present These observations lead to two conclusions·

1 In many cases with diastolic overloading of the right ventricle, incomplete or complete right bundle-branch block is present

2 In a number of cases with diastolic overloading

of the right ventricle, incomplete or complete right bundle-branch block is obscure or absent

A final corollary which must be kept in mind is that many other conditions without diastolic overloading of the right ventricle may show incomplete or complete bundle-branch block patterns. These observations emphasize that there are many pitfalls in the diagnosis of diastolic overloading of the right ventricle This is in contrast to systolic overloading of the R.V. where there are fewer limitations.

For the above reasons, one cannot establish with certainty the diagnosis of diastolic overloading of the right ventricle by the electrocardiogram alone, although sometimes such a diagnosis may be suggested. For example, if an electrocardiogram belonging to a child below 10 years of age shows incomplete R.B.B B and the unipolar pattern of the right ventricle is recorded as far to the left as V_5 or V_6, right ventricular enlargement, D.O R V and atrial septal defect are the most likely possibilities.

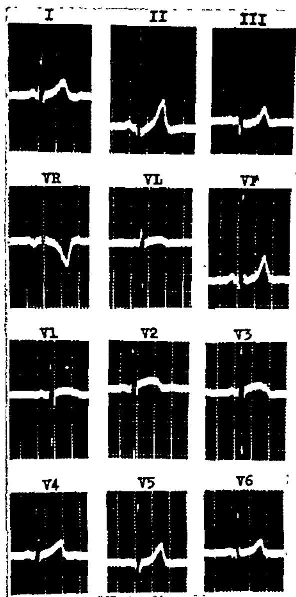


FIG 17—Tracing suggestive of left ventricular enlargement with diastolic overloading of the left ventricle

In children and in infants in whom the diagnosis of D O.R.V. may be formulated, due to the presence of R.B.B B, one must keep in mind other possibilities in which the hemodynamic condition does not correspond to D.O.R.V:

1 Ebstein's disease In addition to the clinical findings, often the electrocardiographic tracing is characteristic, since the deflections related to the free right ventricular wall are recorded only in a few precordial leads or are even absent In addition, the deflections of the right atrium and those of the free left ventricular wall are seen in several precordial leads Because of this, the differentiation from atrial septal defect is relatively easy

2 Rheumatic heart disease with mitral valve involvement Although incomplete R B B B is a common finding, the electrocardiographic pattern is quite different from that seen in atrial septal defect The changes in the P wave, the low QRS voltage in the right precordial leads, the complexes on the left precordium of the RS or rS type, all are items which help to make the differential diagnosis The clinical findings, however, are still the most important

3 In normal hearts (from the clinical and radiographic point of view) it is relatively common to see incomplete or complete R B B B, where, of course, there is no diastolic overloading

Left ventricular enlargement with diastolic overloading of the left ventricle (D O.L.V.). In addition to the electrocardiographic signs of left ventricular hypertrophy (L.V H) in these cases, there are changes in the RS-T segment and T wave which suggest diastolic overloading of the left ventricle (D O.L.V). The changes consist of a slight positive displacement of the RS-T segment with upward concavity, followed by a symmetric, tall and peaked T wave (FIG 17).

A congenital defect which exemplifies this situation is patent ductus arteriosus, an anomaly in which the electrocardiographic pattern described above is often observed in those

leads which reflect the potential variations of the left ventricle (V_5, V_6 and usually II, III, and V_F) Arteriovenous fistulae, aortic insufficiency, tricuspid atresia and ventricular septal defect are conditions with diastolic overloading of the left ventricle in which the pattern described may or may not be present.

There are, however, many other conditions without D O L.V., but with a similar electrocardiographic pattern. These possibilities must be kept in mind in the differential diagnosis. The main ones are:

1 Hyperpotassemia Here the peaking of the T wave involves most of the precordial leads and is not limited to V_5 and V_6; the RS-T segment is isoelectric and sometimes slightly negative; finally, the other electrocardiographic signs of hyperpotassemia outlined before may be present

2 *Subendocardial ischemia.* This is generally seen in adults or old patients with signs that suggest coronary insufficiency (negative RS-T displacement, negative T waves in other leads, left bundle-branch block, etc)

3. Hypervagotonia The pulse rate is very slow, the P waves and P-R intervals are prolonged and the patients are in the second or third decade of life.

4 Pericarditis There is concave positive RS-T displacement, and the peaked tall T wave is a transitory one, changing to a negative T wave of the ischemic type.

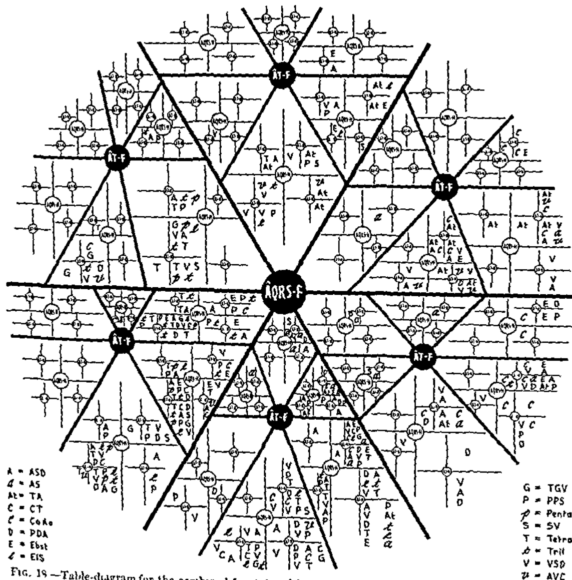


FIG. 18 —Table-diagram for the combined frontal and horizontal representation of both QRS and T vectors for the electrocardiographic classification of congenital heart lesions.

of the right ventricle, incomplete or complete right bundle-branch block is obscure or absent

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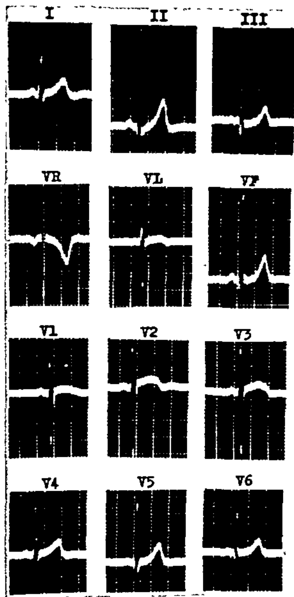


FIG 17—Tracing suggestive of left ventricular enlargement with diastolic overloading of the left ventricle

Left ventricular enlargement with diastolic overloading of the left ventricle (*D.O L.V.*). In addition to the electrocardiographic signs of left ventricular hypertrophy (L V H.) in these cases, there are changes in the RS-T segment and T wave which suggest diastolic overloading of the left ventricle (D O L V) The changes consist of a slight positive displacement of the RS-T segment with upward concavity, followed by a symmetric, tall and peaked T wave (FIG. 17)

A congenital defect which exemplifies this situation is patent ductus arteriosus, an anomaly in which the electrocardiographic pattern described above is often observed in those

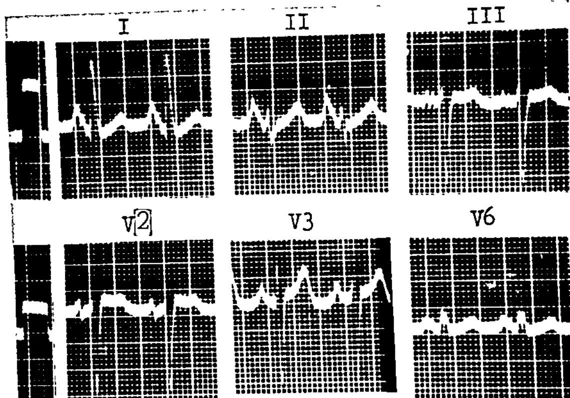


FIG 20—Electrocardiogram of a patient whose proved clinical diagnosis was tricuspid atresia

V_2 and the positive QRS in V_6 places the ÂQRS-H in the first quadrant. Finally the positive T wave in V_2 and V_6 places the ÂT-H in the fourth quadrant

Thus the indicated location is in QRS-F sextant 1, T-F sextant 6; QRS-H quadrant 1, and T-H quadrant 4 Here are seen the symbols for six possible conditions which might give such an electrocardiogram. tricuspid atresia (At), coarctation of the aorta (C), atrial septal defect (A), ventricular septal defect (V), aortic stenosis (a), and atrioventricularis communis (v) The proved clinical diagnosis in this patient was tricuspid atresia.

The scope of the subject is so wide that no attempt has been made to make this chapter "all-inclusive" We have attempted to explain some of the basic postulates of electrophysiology and to relate these to electrocardiography and vectorcardiography. We have further attempted to demonstrate some of the ways in which electrocardiography and vectorcardiography can be used as aids in the diagnosis and management of patients with cardiovascular diseases.

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Left ventricular hypertrophy with systolic overloading of the left ventricle The electrocardiographic pattern is the same as that of the left ventricular hypertrophy alone, systolic overloading of the left ventricle does not give a typical tracing

Congenital Heart Disease

A new method for diagnosis of congenital heart disease recently described by us[19] is based on the frontal and horizontal location of the QRS and T vector angles (ÂQRS and ÂT).

FIGURE 18 diagrams the entire system which represents some extensions of Bayley's triaxial reference system to which has been added horizontal quadrant vectors This apparently can be more easily understood if the four stages of the matrix are discussed individually:

1 The first stage is the large triaxial diagram of the vector angle of the QRS in the frontal projection (ÂQRS-F) This makes the initial separation into the six large sextants emanating from the central black ÂQRS-F circle The first subdivision of an electrocardiogram, therefore, is made into one of the six sextants on the basis of the QRS vectors in the standard limb leads

2 Within each major sextant is a smaller triaxial diagram emanating from the black ÂT-F circle These represent the six frontal T vector sextants for each QRS sextant

TABLE 2—*Key to Symbols for Congenital Cardiac Malformations*

Congenital Malformation	Abbreviations	Abbreviations used in FIGURE 18
Aortic stenosis	A S	a
Atrial septal defect	A S D	A
Atrioventricularis communis	A V C	v
Coarctation of the aorta	Co Ao	c
Common trunk	C T	C
Ebstein's disease	Ebst	E
Eisenmenger's complex	EIS	e
Patent ductus arteriosus	P D A	D
Pentalogy of Fallot	Penta	p
Pure pulmonary stenosis	P P S	P
Single ventricle	S V	S
Tetralogy of Fallot	Tetra.	T
Transposition of the great vessels	T.G V	G
Tricuspid atresia	T A	At
Trilogy of Fallot	Tril	t
Ventricular septal defect	V.S D.	V

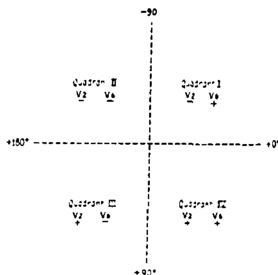


FIG 19 —Horizontal plane seen from above showing the four quadrants considered in this plane, determined by precordial leads V_2 and V_6 (Courtesy of the publisher[1])

3 Within each of the 36 frontal T vector sextants are four larger quadrants emanating from a white circle labeled ÂQRS-H These quadrants represent the direction of the QRS vectors in the horizontal projection The location of the quadrant is dependent on the direction of QRS in leads V_2 and V_6 according to the system diagrammed in FIGURE 19

4 Within each of the 144 horizontal QRS quadrants (ÂQRS-H) are four smaller quadrants emanating from smaller white circles labeled ÂT-H These quadrants indicate the horizontal vector projections of the T waves also according to the quadrant system shown in FIGURE 19

These four steps, therefore, represent 576 small quadrant divisions into which electrocardiograms can quickly be classified Within these quadrants are placed the symbols of the various congenital malformations which might produce the particular combination of electrocardiographic characteristics These symbols are explained in TABLE 2

An example of how an electrocardiogram may be classified is illustrated by FIGURE 20 On the basis of leads I, II and III of FIGURE 20, it can be seen that the frontal QRS vector is −30 degrees, i e , in the first large sextant. Again, on the basis of Leads I, II and III, the frontal T vector (ÂT-F) is +50 degrees which is in the sixth (ÂT-F) segment

Next, we consider the horizontal projection as indicated by leads V_2 and V_6 in FIGURE 20 According to FIGURE 19, the negative QRS in

— 6 —

Phonocardiography

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THE first attempt to record heart sounds was made by Huerthle in 1893 He connected a microphone with an induction coil; this in turn excited a frog nerve-muscle preparation which scratched a tracing on a smoked drum Einthoven and Geluk (1894) replaced the frog preparation with a capillary electrometer and obtained a graphic picture of the first heart sound. Later, Einthoven substituted the recently invented string galvanometer to the electrometer, greatly increasing the accuracy of the method

Modern phonocardiography, unlike modern electrocardiography, had to await the invention of the amplifying triode by De Forest. It was not, however, till the late 1920's that amplifier units for audio work became commercially available. In contrast to electrocardiography, electronic amplification of the vibratory signals in the high-frequency range is essential, if sound phenomenon is to be studied and registered in its entirety. Whereas the mean instantaneous vector of the action potentials of the heart is of such magnitude that it can be clearly registered by a galvanometer of sufficient sensitivity, this is not the case in phonocardiography. In the high-frequency range, the magnitude of the signal is so small that extreme amplification becomes imperative.

The Cardiac Cycle

Contraction of the Atria

The cardiac cycle starts with *the contraction of the atria*, also called "atrial systole." A wave of contraction follows that of excitation, moving downward from above and thus creating a propulsive wave toward the ventricles. Atrial contraction takes place during the short phase which immediately precedes ventricular con-

open during atrial contraction, only a moderate rise in pressure takes place within the atria, and the contraction is mainly revealed by movement of blood.

Contraction of the Ventricles

Initiation of ventricular contraction increases the pressure in the ventricles and closes the *atrioventricular valves* (tricuspid valve in the right heart, mitral valve in the left heart). Immediately afterwards, the contraction of the papillary muscles prevents an eversion of these valves and permits a further rise of pressure to a point first equaling and then exceeding the pressures existing in the aorta and the pulmonary artery. In this short period, the ventricular contraction builds up pressure without causing motion of blood. This short phase is called *period of tension* or *period of isometric contraction* because the muscle fibers of the ventricles build up tension steadily, even though unable to become shorter. As soon as the ventricular pressure exceeds that of the respective artery, the *semilunar valves open* and ejection begins. During this period of outflow or ejection, the fibrous septum which supports the A-V valves is lowered by the contraction of the ventricles. During the last part of ejection, outflow is decreased. Therefore, ejection has been divided into two parts. *maximal ejection*, which includes about one-half of the time, during which the ventricle expels about two-thirds of the blood, and *reduced ejection*, during which the ventricle expels about one-third of the blood in the last half of the time.

Movements of the Valves

Despite their apparently delicate structure, the *flaps of the A-V valves* have considerab

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of this period, e g , following the opening of the A-V valves.

Filling of the ventricles has the following features:

a. An initial phase of rapid passive filling (*early diastole*). This is caused by the difference in pressure between the full atria and the empty ventricles At this time, the entire veno-atrial reservoir experiences a drop in pressure due to acceleration of the stream after the opening of the atrioventricular valves. Elastic recoil of the ventricular wall may accelerate filling (Brecher)

b. A phase of slow passive filling (*mid-diastole* or *diastasis*). The gradual filling of the ventricles slows down the inflow, and a gradual pressure rise takes place in the veno-atrial reservoir as well as in the ventricles.

c. A late phase of rapid active filling (*presystole*) caused by the atrial contraction, which completes ventricular filling. As soon as the atrial contraction is completed, the ventricles start contracting, because the descending stimulus has already reached the ventricular myocardium.

It should be kept in mind that, during ventricular diastole, the atrium and ventricle of each side of the heart behave like a single chamber.

Duration of Cardiac Phases

Certain time intervals may be considered typical of a normal heart (Table 1)

Because of the thinness of the *right* atrial wall and its distensibility, the filling volume of this chamber is about twice that of the *left* atrium

As atrial contraction lasts but a small fraction of the total cycle (less than one-tenth of a second), the atrial wall is relaxed during most of ventricular diastole and during all of ventricular systole. Thus, the atria act as reservoirs for the blood coming to the heart

The traction developed by the ventricular muscles and septum on the atrioventricular junction during systole dilates the atria by causing a phenomenon of suction This is rapidly transmitted to the venous system and accelerates the flow of blood toward the atria

The atrial appendages seem to have little propulsive function and serve as complementary spaces which fill the deep niches at the base of the heart during ventricular systole.

In abnormal conditions, as in cases with rapid heart rate, diastole shortens tremendously In such cases, atrial contraction may include most or all of diastole and acquire much greater importance.

Apparatus

Microphones. Microphones used in phonocardiography convert the vibratory motion of the chest wall either directly or indirectly into deflection of a diaphragm, coil or ribbon. In the indirect method, a closed air chamber is interposed, so that the displacement is transformed into pressure, which then acts on the diaphragm In the direct method, the diaphragm is brought into direct contact with the skin through a connecting rod An original approach described by Groom attempts a perfect capacitive coupling by juxtaposing the skin to a capacitor plate

In the piezo-electric crystal and the capacitor microphone, the electromotive force (E.M.F) generated at any given moment is directly proportional to the deflection of the diaphragm, which in turn is a function of the pressure applied at the input. In both cases, the design of the microphone is such as to insure that the ratio of the deflection to the pressure applied is independent of frequency. In the final analysis, both the crystal and the capacitor microphones are displacement microphones. The displacement of the diaphragm, however, is greatest for the low-frequency components since, for a given pressure, the amplitude decreases with increasing frequency.

Filters A filter is a network whose function is to pass a given band of frequencies without appreciable attenuation, and to attenuate all others The frequency which marks the junction of the pass band and the attenuated band is known as the cutoff frequency. From the standpoint of frequency characteristics, filters are essentially of three types: low-pass filters, high-pass filters and band-pass filters. In the low-pass filters, all frequencies above cutoff frequency are attenuated at a specified rate. In the high-pass filters, those below a cutoff fre-

not merely touch but form a surface contact without folds. Closure is started by the eddy currents and is increased by the ventricular contraction which immediately follows. Eversion is prevented by the chordae tendineae, held by the papillary muscles The musculature of the septum and of the papillary muscles is the first to contract, insuring a timely closure of the valves The termination of atrial contraction contributes to the closure of the A-V valves, because the leaflets are brought into position by the eddy currents set up by the flow through the orifices and by a reversal of the pressure gradient This is shown by the temporary valvular insufficiency which frequently develops in cases with incomplete A-V block. In the event of delayed A-V conduction, *there may be a double closure of the A-V* valves: the first at the end of atrial contraction, the second at the beginning of ventricular systole

The semilunar valves of the aorta and pulmonary artery resemble pockets attached to the wall of the vessel The blood contained in the pockets keeps the valves away from the wall *Both the reversal of the gradient of pressure* created by the sudden cessation of outflow, and the eddy currents cause closure of these valves at the end of ventricular systole Firm attachment of the valves, muscular support from the ventricular base, and lateral apposition prevent any possibility of eversion, in spite of the lack *of chordae tendineae*

Research in normal animals by means of

TABLE 1 —*Time Intervals Between Cardiac Phases (Normal Dogs)*
(in seconds)

	Right heart	Left heart
Ventricular Systole		
Tension	0 02–0 04	0 05–0 06
Ejection	*0 18–0 28*	*0 17–0 26*
Total Systole	0 20–0 32	0 22–0 32
Ventricular Diastole		
Protodiastole	0 02	0 04
Isometric relaxation	0 06–0 08	0 08–0 12
Rapid filling	0.08–0 10	0 08–0 10
Slow filling	variable	variable
Atrial dynamics	0 11–0 13	0 11–0 13

multiple heart catheterizations[25, 26] has revealed the following data (see FIG. 2):

a The interval between beginning of rise of pressure in a ventricle and the crossing of the atrial pressure curve is extremely short (in the range of 0 01 second or less) This indicates that closure of the mitral and tricuspid valves occurs practically at the onset of ventricular systole

b In certain of the cycles, left ventricular pressure rises first and increases at a faster rate Right ventricular pressure lags behind by 0 01 to 0 02 second and rises more slowly It is reasonable to suppose that, in these cycles, mitral closure precedes tricuspid closure by 0 01 to 0 02 second This is confirmed by external and intracardiac phonocardiography In other cycles, the two pressures rise simultaneously, the difference often shown by two subsequent cycles It is likely that, in those cycles, mitral and tricuspid closures occur *simultaneously*

c The rise *of pressure in* the pulmonary artery always precedes that of the aorta The interval is usually in the range of 0 02 second and may become longer or shorter if there is a marked change of pressure in one of the vessels

d The relationship of mitral closure to aortic opening, and of tricuspid closure to pulmonic opening is such that the following isometric periods should be accepted (1) RV —0 02 to 0 04 second, (2) LV—0 05 to 0 06 second Thus, the following sequence of events takes place (1) mitral closure, (2) tricuspid closure, (3) pulmonic opening and (4) aortic opening

e The end of left ventricular systole always precedes that of the right

f The opening of the mitral valve always follows that of the tricuspid This interval is usually between 0 04 and 0 06 second but may reach even 0 08 second.

g Rapid filling of the left ventricle always follows that *of the right* The *interval* between the two is similar to that occurring between the opening of the A-V valves Each peak of rapid filling follows A-V valve opening by 0 08 to 0 10 second, and the closure of the respective semilunar valve by 0 12 to 0 18 second

TABLE 1 shows the sequence of events in normal, large dogs, whose figures are practically identical with those of normal man

VENTRICULAR DIASTOLE

At the end of ventricular systole, ventricular pressure drops to zero Following an extremely brief interval of latency (so-called *protodiastole*) the semilunar valves of the aorta and pulmonary artery close A short time interval separates this phase from the subsequent opening of the A-V valves: the *isometric relaxation period*. Ventricular filling starts after the end

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quency are attenuated, a band-pass filter allows a particular band of frequencies only The desired effect is usually obtained by a combination of high-pass and low-pass filters

Band-Pass Filters A band-pass filter is essentially made of a high-pass and a low-pass filter *connected in series*. Such a filter should incorporate the characteristic of both the high-pass and the low-pass sections

In the operation of a band-pass filter, the interaction of the peaking circuits of both the high and low cutoff should be taken into consideration For a pass band of one octave, however, it should be possible to obtain a band with a zero decibel loss in the center of the band and a 3 decibel loss at the cutoff frequency.

Amplifiers The main function of an amplifier is to magnify and reproduce the essential features of an input wave representing very little energy Since the output represents an *appreciably greater amount of energy*, the amplifier draws power from a source other than the signal The fundamental principles of vacuum tube amplification and design factors need not be elaborated here as they are well known. On the other hand, the design or selection of an amplifier, particularly suited for phonocardiographic work, requires great attention paid to those desirable characteristics and specifications which have a direct bearing on the amplified signal. Amplifiers can be broadly classified into separate classes depending on the region of the tube characteristics in which they operate When the operation is *linear* (i.e , restricted to the linear region of the tube characteristics), the input and output voltages are linearly related, and the amplifier is designated as Class A amplifier

Oscillographs. The recording oscillograph represents the final, or transcription, stage of the phono system The small current and voltage variations which are transduced, amplified and filtered are then transferred to a photosensitive record (via the oscillograph), where they can be measured and studied individually and comparatively.

Recording oscillographs in use incorporate as the recording arm either a galvanometer or a cathode-ray tube. The cathode-ray tube is undoubtedly the most accurate and sensitive recording device. Unlike all other means of recording, it is free from the effect of inertia, and hence its frequency response is unlimited In conjunction with a blue fluorescence of high actinic value, it is ideal for photography, since a slow paper can be used with good results In conjunction with a phonocardiographic system, however, the cathode-ray tube may prove less than ideal because of the limitation on the brightness of the spot when high frequency vibrations are being inscribed, since, the faster the spot moves, the fainter the trace becomes.

Accurate reproduction of the individual vibrations of a sound or murmur requires rapid film motion This should be between 75 mm per second and 150 mm. per second Speeds lower than 75 may be useful for giving a visual impression of the "shape" of a murmur but not for an accurate study

Certain specific instruments should be mentioned because of their different and representative characteristics

Sanborn twin-beam Based on the studies of Rappaport and Sprague, this apparatus can record three different types of tracings: linear, stethoscopic and logarithmic The linear tracing records unchanged the vibratory phenomenon of the chest wall and is suitable for the ultra low-frequency vibrations (1 to 10) on account of their relative magnitude. The stethoscopic tracing presents a picture in which the relatively low-frequency vibrations (25 to 50) predominate, it has the advantage of giving a good over-all picture of the heart sounds but is inadequate for recording most soft murmurs The logarithmic tracing has a frequency response similar to that of the human ear but is still not perfect in the reproduction of very soft murmurs

Cambridge phonocardiograph. The conventional apparatus was developed over 25 years ago and gives a tracing which is similar to the logarithmic tracing of the twin beam Extra sounds and low-frequency murmurs are poorly recorded. Many of these disadvantages have been corrected in the large audio-visual apparatus which is employed for teaching or presentation to large groups.

Elema phonocardiograph. This is based on the use of high pass filters, following the work

of Mannheimer. It has several advantages. Among the disadvantages are that it is a direct-writing system (even though the transcription is most accurate having no attrition), and that there is a fixed compensation for the physical attenuation of high-frequency vibrations This sometimes leads to poor transcription of high-frequency vibrations

Selective phonocardiograph. This was described by Luisada et al.[22] and consists of the addition of a Krohn-Hite variable band-pass filter to the Sanborn "stethoscopic" system. It supplies excellent records in any band up to 500 cps and lends itself to routine studies. It has the disadvantage that one cannot record an ECG as a reference tracing with it (FIGS. 4, 6–11A, 12–14)

Linear and calibrated phonocardiograph. This was described by Luisada and Zalter[28,42] It is built with parts of the Altec-Lansing Company (microphone, amplifiers), the Krohn-Hite Company (variable band-pass filter) and the New Electronic Products, Ltd. (galvanometers, camera). It gives most satisfactory results from 10 to over 1,000 cps. The tracings are recorded in bands of one octave (except in the high frequency, where one-half an octave seems preferable) The most important bands for routine clinical studies are three the 60 to 120, the 120 to 240 and the 240 to 480 cps (FIGS. 3 AND 11B).

The Laws of Auscultation

It is well known that the auditory system of man is not ideally suited for cardiac auscultation Knowledge of its limitations may explain some of the pitfalls of auscultation and certain unavoidable discrepancies between clinical impression and objective data. These limitations may be summarized as follows

Pure tones of different pitch and the same intensity are heard like tones of different intensity

The ear detects more easily changes of pitch than changes of intensity (except in the lower frequency range where changes of pitch may not be detected at all) As a result, a higher pitched tone of the same intensity is heard as a louder tone

The ear cannot appreciate vibrations having a frequency below 20 per second or an intensity below 0.0002 dyne per cm.² In addition, sensitivity to the low-pitched vibrations is extremely poor (unless they have a great intensity) and gradually increases for the higher frequencies.

The normal heart is the source of vibrations which are normally between 1 and 500 per second while cardiac murmurs may occasionally reach 800 vibrations per second and occasionally more. It should be kept in mind that, on account of low intensity of the vibrations, 90 per cent of them are below the limits of audibility and could be named *infra-sounds*, while a good percentage of the others is in the borderline or *subliminal* range, so that they are heard only by particularly well trained observers

The scale of sensitivity of the ear with regard to frequency increases very rapidly, on a logarithmic ratio. It is only at the frequency of 1,000 cycles that a given increase of intensity results in the same increase in loudness In lower frequency bands, much larger increases of intensity are necessary in order to cause the same phenomenon

In the presence of certain large or high-pitched sounds, the ear may be unable to detect small or low-pitched sounds which follow immediately. This phenomenon is called "masking."

THE NORMAL HEART SOUNDS IN HUMAN SUBJECTS

The phonocardiogram of a normal subject may record up to four main heart sounds and occasionally more The two louder sounds are called the first and second sound (FIG. 1), the others, the third and fourth sound (FIG 2)

The first heart sound occurs at the beginning of ventricular systole and lasts through the tension period and the beginning of the ejection period The second heart sound is shorter, it takes place at the end of systole, during the phases of protodiastole and isometric relaxation The term "systolic sounds" has been suggested by one of the authors for these two constantly heard sounds The other two sounds, less frequently heard, take place dur-

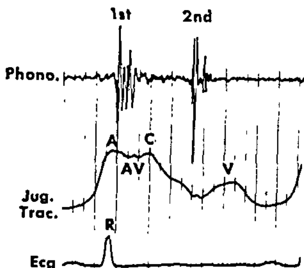


FIG 1.—(*From above*) Heart sounds of a normal subject recorded with a Peiker microphone and a filter in the band 60–120 jugular tracing ECG Four vibrations are visible within the first sound

ing diastole. The term "diastolic sounds" has been suggested for them

The following dynamic phenomena coincide with the heart sounds (see also TABLE 2)

Systolic Sounds

First Sound.

Initiation of ventricular systole.
Closing of the A-V valves
Opening of the semilunar valves
Beginning of ejection.

Second Sound.

End of ventricular systole
Closing of the semilunar valves.
Opening of the A-V valves

Diastolic Sounds

Third Sound Peak of rapid passive filling of the ventricles

Fourth Sound: Peak of rapid active filling of the ventricles due to atrial contraction

Since the cardiac chambers are filled with blood, none can vibrate without producing movements or vibrations in the blood which they contain. Therefore, the cardiac walls, the valves, the arterial walls and the blood represent an interdependent system which vibrates as a whole (Rushmer).

The *first sound complex* is caused by a complex musculovalvular mechanism, and it is impossible to attribute any separate vibration to a special factor (valvular, muscular, etc.) However, two groups of taller vibrations were recorded even by old type phonocardiographs The coincidence of the first group with the beginning of ventricular systole and of the second with the rise of the carotid pulse was accepted as evidence that the former was due to vibrations of the heart coinciding with A-V valves closure, while the second was due to vibrations coinciding with semilunar valves opening[15] (FIG. 3). An alternate interpretation, which was not supported by convincing evidence,[5] attributed the first group to mitral closing, the second to tricuspid closing.

Recent phonocardiographic studies obtained by means of a Peiker microphone and a cathode-ray oscilloscope have demonstrated *four* main vibrations within the first sound complex[27] (FIGS 1 AND 3) Intracardiac pressure tracings and intracardiac and extracardiac phonocardiograms have revealed that each of them coincides with a valvular motion in the following order (FIG 2): mitral closure—tricuspid closure (first group of two), pulmonic opening—aortic opening (second group of two).

This sequence has been confirmed by Lewis et al [10] with an intracardiac microphone and by Gribbe et al. with cineradiography.

Physiologic splitting of the first sound in normal hearts is caused by greater separation of the two main groups (A-V closures, then semilunar openings), a fact which becomes particularly apparent if one records the sounds at the midprecordium (so-called "tricuspid area") in the band 200 to 400 cps (FIG 3)

The *second sound* is usually simpler and shorter Its main group of vibrations is due to closing of the semilunar valves, and a study of these vibrations can give information about the function of the aortic and pulmonic valves Usually, the aortic valve closes first, the pulmonic later An asynchronism of 0 02 to 0 03 seconds between aortic and pulmonic closure is revealed by recording the tracing in the second or third left interspace in the band 200 to 400[8]. The first, larger vibration is aortic, the second, smaller, is pulmonic (FIG. 1). Following these vibrations, small notches, due to the opening of the A-V valves, can be observed. If there are two of them, the first in-

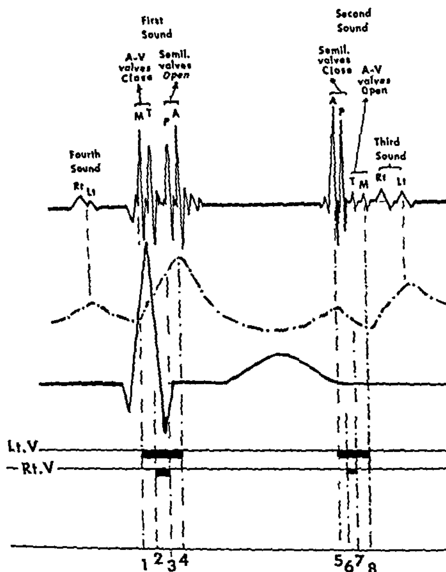


FIG 2 —The four valvular events and their sequence are revealed in normal dogs and in humans by pressure curves plus intracardiac and extracardiac phonocardiograms Scheme comparing sound vibrations with an ultra low frequency tracing and an ECG

TABLE 2—*Time Intervals Between Valvular Motions (Normal Dogs)*

Event	Interval (in seconds)	Symbol	Heart Sound
Q wave (ECG)	0 06-0 07		
Closure of mitral valve	0 00-0 02	M	
Closure of tricuspid valve	0 01-0 03	T	First sound major vibrations 0 06-0 08
Opening of pulmonic valve		P	
Opening of aortic valve	0 01-0 02	A	
Closure of aortic valve	0 02	A	
Closure of pulmonic valve	0 03-0 04	P	
Opening of tricuspid valve	0 04-0 08	OT	Second sound major vibrations 0 04-0 05
Opening of mitral valve	0 -0 04	OM	
Rapid filling of right ventricle		3R	
Rapid filling of left ventricle	0 04-0 08	3L	Third sound

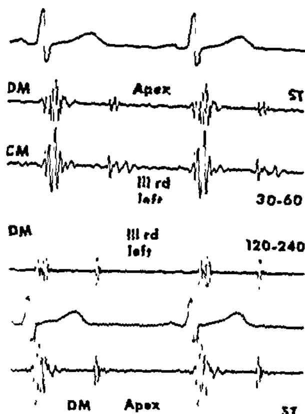


FIG 3 —Phonocardiograms recorded with a new system in a normal young man of 17 DM = dynamic microphone, CM = capacitor microphone (Above) The lower tracing (lower frequency band) reveals four vibrations within the first sound (Below) The upper tracing (higher frequency band) reveals two groups of vibrations simulating a splitting of the first sound

dicates tricuspid opening, the second mitral opening Mitral opening frequently becomes loud, snapping and delayed in mitral stenosis (opening snap of the mitral valve) giving the auditory impression of a reduplicated second sound.

The *third sound* and the *fourth sound* usually consist of one or two small, low-pitched vibrations which are recorded best in the band 30 to 60 cps. (FIG. 4) The third sound is often recorded in children, young adults or persons with a thin, flat chest. Two alternative theories have been advocated for this dull sound. The first, advocated by Thayer (1909) and by Dock (1956), attributed this sound to a vibration of the mitral valve, while other authors related the sound to an impact of the apex on the chest wall. A second theory explained it as due to vibrations of the ventricular walls at the time of rapid filling on account of the onrush of blood from the atria to the ventricles The perfect coincidence between third sound and peak of the phase of rapid filling seems to confirm the last theory. Revival of the concept of *active diastole* of the ventricles might lead to speculation that the sound takes place at the end of the phase. Experiments in dogs reveal that rapid filling takes place earlier in the right than in the left ventricle

The *fourth sound* takes place in presystole and is due to vibrations of the ventricular walls which occur when blood is forced into the ventricles by atrial contraction. Comparison of the fourth sound recorded by way of the esophagus with the recorded sound at the apex revealed that, while early vibrations of the esophageal tracing could be attributed to the atrial contraction per se or to valvular vibrations, the vibrations recorded at the apex occur later and could be explained only with ventricular vibrations (Orias and Braun Menendez, 1939).

Increased magnitude of either the 3rd or the 4th sound is the most common cause of the "triple rhythms" (so-called *gallop rhythms*).

Duration of Heart Sounds

First sound complex The division of the first sound into five parts has important theoretical

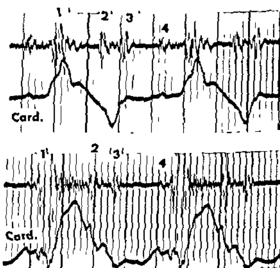


FIG 4 —Phonocardiograms (stethoscopic) and ultra low-frequency tracings of the apex in two children with acute rheumatic fever (*Above*) There is a large third sound and a medium-sized fourth sound. (*Below*) There is a systolic murmur, a large third, and a normal fourth sound

implications, however, a simplified method has practical advantages.[14] The main portion of the sound is made of large, irregular vibrations (Parts II, III, IV) while the beginning (Part I) and the end (Part V) are made of slower vibrations. It is not always easy to locate the beginning and the end of these two phases, especially the last. Therefore, it was suggested that the sound be divided into only three phases: (1) initial, slow vibrations, (2) central, large vibrations, and (3) final, slow vibrations.

The *total average duration of the first sound* at the apex with the stethoscopic system for ages above 10 years is 0.140 second. The maximum total duration of the first sound complex at the apex is 0.16 between 11 and 20, and 0.22 in the older groups. The average duration of the *second* (or central) phase of the first sound at the apex is 0.06 second for ages above 10 years. The maximum duration of the second (central) phase is 0.12 in the group 11 to 20, and 0.10 in the older groups. Figures above these reveal the existence of a systolic murmur.

Second sound complex. The second sound is frequently longer in graphic tracings than it seems at auscultation. It is caused by the closure of the semilunar valves of the aorta and pulmonary. The subsequent opening of the A-V valves may add small vibrations. Four parts or components can be distinguished within the complex. However, for practical considerations, it was suggested[18] that this complex be divided into three phases only; the second, or central, phase made of large vibrations is the most important for clinical purposes.

The *total average duration* of the second sound at the base with a "stethoscopic" system is 0.12 second in the age group 11 to 20. The average duration of the second (central) phase of this sound is 0.055 in the age group 11 to 20. The maximum duration is 0.16 second for the total sound and 0.10 for the second (central) phase, in the age group 21 to 40.

Special tables outlining the duration of heart sounds for normal children have been prepared by Aravanis and Cardi,[1] and, for old persons, by Aravanis and Harris.[2a]

Intervals Between Heart Sounds

The normal heart sounds are separated by intervals which do not exceed certain limits and which may help in the recognition of extra sounds.

The *interval between the beginning of the fourth sound and the beginning of the first* may be as short as 0.05 second at the base between 41 and 60 years of age, and as long as 0.072 at the apex in persons between 21 and 40 (unless there is A-V block). The over-all average is 0.058 on all areas of the precordium. Children of various ages have different data.

The *interval between first sound and second sound* varies according to the various lengths of ventricular systole. The duration of electrical systole varies according to the heart rate, the mechanical systole is slightly shorter than the electrical and can be reckoned as the length of electrical systole minus one-half of the duration of QRS; in other words, mechanical systole is about 0.04 to 0.05 second shorter than electrical systole.

The *interval between the third and fourth sounds* varies considerably according to the duration of ventricular diastole. If diastole is short, as in tachycardia, this interval may disappear altogether and there may be a "summation" type of triple rhythm.

Interval second-to-third sound. This interval is usually between 0.14 and 0.18 second in adults but may be between 0.10 and 0.15 in children.

Interval between the components of the second sound. The second sound is normally composed of two phases or components, the first is aortic, the second, pulmonic. These components normally approach in expiration and become more widely separated in inspiration (variable splitting). The interval is from 0.02 to 0.05 second in adults.

The interval Q-to-1. This interval is measured between the beginning of the Q wave of the ECG and the largest vibration (mitral closure) of the first sound. This interval is normally below 0.08" in adults. It is severely prolonged in mitral stenosis, less markedly in cases of myocarditis, rheumatic fever, hypertension etc. It is typically variable in cases of mitral stenosis with atrial fibrillation, where it is inversely related to the length of the previous diastole (longer diastole equals shorter Q-1).

Interval 2-to-OS. This interval is measured

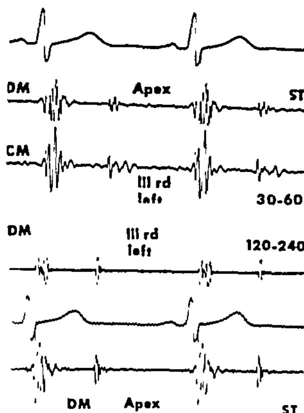


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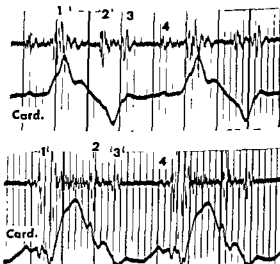


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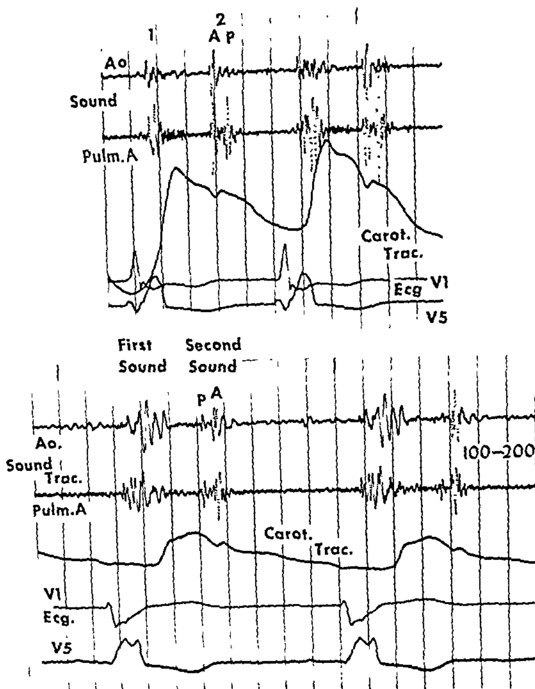


FIG. 5—Two cases of bundle branch-block with split second sound. (*Above*) RBBB, common type of splitting with delayed pulmonic component. (*Below*) LBBB, unusual (so called paradoxical) type of splitting with delayed aortic component.

pitched and may be recorded over the entire precordium, even though it is usually recorded best over the third and fourth left interspaces.

Splitting of the First Sound

Apparent splitting of the first sound may occur whenever the higher frequency components of this sound are widely separated. This may be physiologically noted if the tracing is recorded over the midprecordium (third left interspace) and is due to separation of the mitral-tricuspid closing vibrations (first group) from the aortic-pulmonic opening vibrations (second group; FIG. 3). This splitting may

from the peak of the aortic component of the second sound to the peak of the opening snap (see below). Thus, it is possible to measure it, with few exceptions, only in mitral stenosis. It measures from 0.06 to 0.12 second. High left atrial pressure or commissurotomy abbreviates it. Severe narrowing of the valve prolongs it. This interval varies in cases with atrial fibrillation, where it is directly proportional to the level of pressure in the left atrium and therefore to the length of the previous diastole (longer diastole equals longer 2-OS)

Triple and Quadruple Rhythms

The name "triple rhythm" has been suggested to indicate that cadence of the heart sounds which is caused by the addition of *one* extra sound to the two, more commonly heard, sounds.

Phonocardiography has revealed the frequent occurrence of diastolic sounds in tracings of normal subjects in whom auscultation revealed only a two-sound rhythm (a diastolic sound may not be audible because it is low-pitched, weak or too near the first sound) Therefore, triple rhythms may be either physiologic or pathologic, and the diagnosis should be made on the basis of graphic data [13]

Diastolic gallop (Triple rhythm caused by addition of a diastolic sound). Three types have been recognized

1. Ventricular type. It is caused by increased loudness or high pitch of the third sound, which takes place in early diastole at the time of rapid ventricular filling (Fig 4) It is not unusual in normal subjects under the age of 40, but it is more commonly observed in the presence of tachycardia or diastolic overload of one ventricle (mitral or aortic insufficiency, atrial septal defect) Whenever it is found in subjects over 40, it represents evidence (
favora
sound
tis, where the extra sound occurs early in diastole (about 0 10 second after the second sound) and is large and high pitched The extra-sound always coincides with the peak of the phase of rapid filling.

2. Atrial type. It is caused by increased loudness or high pitch of the fourth sound, which takes place in *presystole*, at the time of the atrial contraction. It is not uncommon, even in normal subjects, over the age of 40 Its audibility is favored by prolongation of the A-V conduction. It is more common in coronary or hypertensive hearts with ventricular strain and increased left atrial pressure It represents the result of some degree of left ventricular failure with atrial engorgement and indicates a less favorable prognosis

3 Summation type. It is caused by the summation of the third and fourth sound in *mid-diastole due to severe tachycardia*; the resulting sound is complex and prolonged.

In cases with a diastolic type of triple *rhythm, slowing of the heart or decrease of* the ventricular load may cause disappearance of the extra sound

Whenever both the third and the fourth sound are loud and high pitched, a *quadruple rhythm* takes place. This requires a relatively *slow heart beat and a condition of ventricular* strain with some engorgement of one or both the atria.

Systolic gallop (triple rhythm caused by addition of a sound in systole). Several types have been described

1 *There may be addition of a* sound of medium pitch in early systole, over either the aortic or the pulmonic areas * It is due to vibrations arising in the vascular walls because of increased pressure in, or pathology of, one of the larger arteries

2 There may be a loud and rapid vibration near midsystole, usually heard and recorded best at the apex. It has been attributed to traction of pleuropericardial or diaphragmopericardial adhesions (Fig 5).

Triple rhythm caused by increased loudness of the opening sound of mitral valve. In mitral stenosis, there frequently is present a loud snap, coinciding with and caused by the opening of the stenotic mitral valve This sound is high-

* This sound is a normal phonocardiographic finding if small and may become audible if of great magnitude (Luisada, 1948) It should not be confused with the "opening click" of the aortic or pulmonic valves, which occurs earlier (at the end of the first sound) and which will be described below

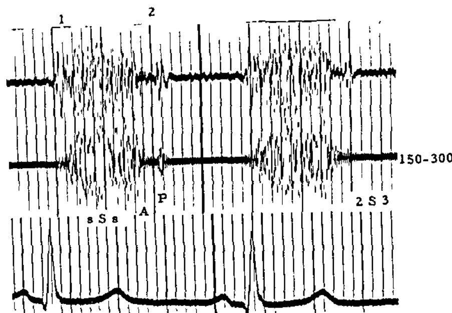


FIG 6 —Woman of 29. Moderate infundibular pulmonic stenosis Ventricular septal defect, right-to-left shunt (catheterization) Delayed and attenuated pulmonic component of the second sound All systolic murmur overlapping the aortic component of the second sound. In this, like in all subsequent tracings, a band-pass filter was used. Its slopes can be described, according to an international agreement as (−3 db)/36

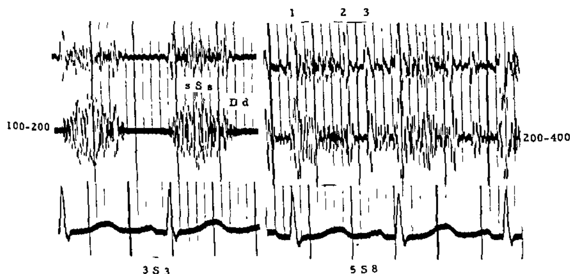


FIG. 7.—
tion). Large
and short,

hypertension would decrease the delay or even mask it.

MURMURS

General Characteristics

The frequency characteristics of the murmurs have been the object of several investigations Cabot and Dodge, and Williams and Dodge, listening through electric filters, recognized that, while low-pitched murmurs had vibrations in the range of from 120 to 400 cps, 9 out of 11 cases had vibrations below 120. The high-pitched murmurs had vibrations between 240 and 400 cps, with some reaching up to 660

occasionally become audible but should be considered abnormal only if the two groups of vibrations are separated by more than 0 04 to 0 05 second. An apparent splitting is recorded (and is also heard) beyond the usual area when there is an abnormality in either the aortic or the pulmonic valve Then, the usually moderate vibrations which accompany the *opening of the valve become extremely* large (*opening click* of the aortic or pulmonic valve, described by Gallavardin, by Lian and co-workers, and by others, and reemphasized by Leatham.*[9]) This click can be recorded over the aortic area in cases with fibrosis or calcification of the aortic valve and moderate stenosis, occasionally, in cases with aortitis or hypertension. It can be recorded over the pulmonic area in cases of moderate pulmonic stenosis or pulmonary hypertension and also, though not in all cases, in the tetralogy of Fallot Such a group of vibrations, which occur at the end of the central phase of the first sound (phase of the large, *medium or high*-pitched vibrations) should be differentiated from the lower pitched vibrations (These occur *normally at the end of the first sound and* usually become larger in cases with aortitis, hypertension or dilatation of the aorta or pulmonary artery) Records are best obtained with a "stethoscopic" system (see above)

Splitting of the first sound may occur in bundle-branch block. However, the most common occurrence (Fig 5) is that of a low-pitched, prolonged first sound, which simulates a murmur upon auscultation (Luisada and Contro[17]).

Splitting of the Second Sound

In normal subjects, the pulmonic component of the second sound takes place 0.02 to 0.03 second after the aortic component.

Splitting of the second sound is caused by asynchronism of closure of the aortic and pulmonic valves. As the pulmonic component is fainter and has a poor transmission, a split second sound is usually heard only over the second left interspace, which is near to the anatomic projection of both the aortic and pulmonic valves *On the other hand, the* graphic tracings at times show a split second sound over a much wider area

Physiologic splitting is frequent in children and occasionally found in adults, with periodic occurrence due to respiration the smaller pulmonic component is periodically delayed in inspiration (Figs 1 and 2)

In *mitral stenosis*, splitting of the second sound is frequent The high pressure of the pulmonary circulation leads to longer duration of right ventricular systole, so that the loud pulmonic component falls after the aortic component In chronic cor pulmonale, as well as in primary *pulmonary hypertension*, a similar mechanism may cause splitting of the second sound In atrial septal defect, a constant splitting *of the second sound, due to increased* flow of the right heart and prolonged right ventricular ejection, is the rule (Fig 8)

In *pulmonic stenosis*, the pulmonic component is small and delayed (Fig 6) Should one set the end of systole at the time of the large (aortic) second sound, then the pulmonic component would seem to fall in early diastole.

In *aortic stenosis*, the aortic component is typically small and delayed and falls 0 02 to 0 04 sec. after the pulmonic component (so-called paradoxical splitting)

In *bundle-branch block*, splitting of the second sound (Fig 5) is the rule (22 out of our 24 cases). In right bundle-branch block, delayed activation causes delayed contraction of the right ventricle, the pulmonic component of the second sound falls from 0 04 to 0 08 seconds after the aortic component Pulmonary hypertension would exaggerate the interval between *the two components* In left bundle-branch block, delayed activation causes delayed contraction of the left ventricle; the aortic component *of the second sound falls from* 0 02 to 0 04 second after the pulmonic component (so-called paradoxical splitting). Systemic hypertension would increase the delay, pulmonary

* Leatham called this sound "ejection sound " The authors believe that such term is inaccurate because the vibrations coincide with the opening of the valve and precede the most important part of the phase of distention of the vessel Instead of being an entirely new phenomenon, this click represents the intensification of a *group of* vibrations which already occur in normal conditions

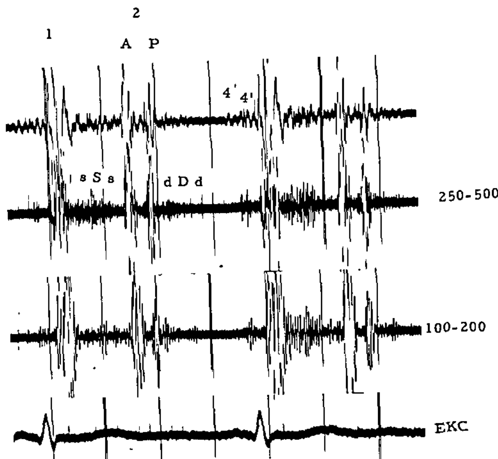


FIG 8.—Woman of 45 with atrial septal defect and pulmonary hypertension (catheterization) Constant and wide splitting of the second sound Moderate systolic murmur Double fourth sound Early diastolic murmur

with predominance of the higher. It is typical of moderate mitral regurgitation and is recorded best at the apex

4 *Low-grade, all systolic murmur*, usually made of high-pitched vibrations. It lasts throughout all systole but does not cover the second sound. It is recorded mostly at the apex and occurs in mitral regurgitation, especially in children (FIGS. 6 AND 9).

5. *Diamond-shaped or pulse wave-like murmur*, typically recorded at the base. The vibrations start soon after the end of the first sound, increase toward the middle of systole and decrease later. They are made of various frequencies with predominance of the medium range (FIGS 6–9 AND 13). The murmur is typical of absolute or relative stenosis of the aorta or pulmonary artery The peak of the murmur corresponds to that of the pulse in the carotid tracing. In "relative stenosis," the peak of the murmur is usually in the first half of systole, while in organic stenosis the peak falls *after* the middle of this phase This fact is particularly apparent in severe stenosis, where the peak occurs late in systole Congenital aortic stenosis, being usually of the subaortic type, may represent an exception (see below).

6. *Concertina-like murmur*. The vibrations show phases of louder and lower intensity, all within a rather narrow band of frequencies. The murmur has the maximum intensity over the midprecordium, is rather musical and spreads in several directions It is found after a myocardial infarct (rupture of a chorda, mural thrombi), in ventricular septal defect, and in calcific aortic stenosis.

7. *Crescendo systolic murmur*. It may be found at the base in severe pulmonic or aortic

and occasionally 1,000 per second In each *individual case, a large percentage of the total* energy was in a relatively narrow band.

With a similar method of filtering, and listening to cardiac murmurs, Butterworth et al[2] found that the predominant frequencies of most systolic murmurs were between 80 and 120 cps, those of most mitral diastolic murmurs were between 40 and 100, and those of most aortic diastolic murmurs were between 100 and 200

Luisada et al.[21] made a graphic analysis of murmurs by means of a variable band-pass filter with similar results Most vibrations of *clinical importance were found in the low- frequency* and medium- frequency bands. Even in cases having "high-pitched" vibrations (600 cps or more), there was such a predominance of energy in the vibrations below 200 that the best tracing was often that recorded between 150 and 200 Frequencies above 400 cps were recorded only with marked amplification, and those above 600 were of minimal importance *and difficult to register Only recently* was it possible to register with accuracy very high-pitched murmurs[29a] Vibrations in the range between 500 and 1000 cps were found rather often in cases with soft, high-pitched basal murmurs, between 1,000 and 2,000, in exceptional cases, especially if the patients had a flat chest

The frequency characteristics of a sound or *murmur can be analyzed also in a different way* A special device, utilized by McKusick, transcribes vibrations of higher frequencies as vibrations of greater height.[30] This method was called "spectral phonocardiography"

It utilizes a device originally developed at the Bell Laboratories by Fletcher (sound spectrograph) for the study of speech frequencies and intensities It is based on the tape recording of a few cardiac cycles within 2 5 seconds and on the successive rapid, automatic scanning of these cycles by means of a variable filter during 15 seconds The final tracing reproduces vibrations of different frequencies on a graph, the ordinate of which represents frequencies, while the abscissa represents time This method, which is technically still in its infancy, *yields promise for special studies*

Cardiac murmurs are transcribed as complex groups of vibrations. It is easy to decide whether these vibrations are low-pitched (more separated) or high-pitched (near and packed together), whether they correspond to a rumble (sparse and irregular vibrations) and whether the murmur is musical (regular vibrations) The relationship of these vibrations to the heart sounds indicates whether the murmur is systolic, early-diastolic, or presystolic.*

The graphic disposition of the vibrations has led to recognition of several types of murmurs according to their "shape". In many cases, the "graphic shape" of a murmur, which can only be guessed by auscultation, has a diagnostic significance

While this "shape" can be easily observed on an average tracing, a special device gives an automatic contour of the murmur—sonvelography[25] The sonvelograph transforms the heart sounds and murmurs into "envelopes" proportional to the logarithm of sound intensity

Systolic Murmurs

A systolic *murmur is revealed by* the phonocardiogram as a series of vibrations of different pitches Only in certain cases does the tracing present regular vibrations of the same frequency; then, auscultation reveals a "musical," or "sea-gull cry" or "dove-coo" type of murmur (FIG 14)

The following types of systolic apical murmurs can be observed:

1 *Prolongation of the second phase of the first sound* in spite of the fact that the over-all length of the sound is still within average or maximal limits.

2 *Prolongation of the total duration of the first sound*, which lasts beyond the peak of the C wave of the jugular tracing or the peak of the main wave of the carotid tracing The murmur is more prolonged

3 *Murmur in decrescendo.* This has larger vibrations at first, smaller vibrations later. It usually ends long before the second sound. It is composed of vibrations of different pitches

* The term mid-diastolic murmur is frequently inaccurate if used for description of graphic tracings of diastolic murmurs A murmur is a prolonged series of vibrations Only in rare cases is diastole so long and the murmur so placed that such a term is justified

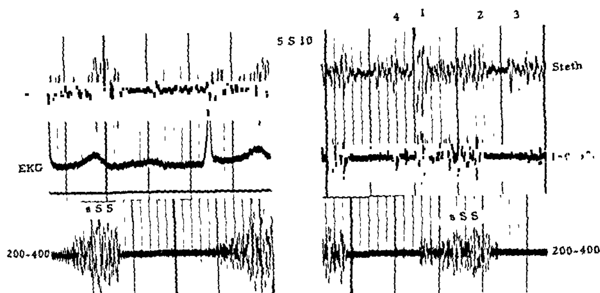


FIG 10 —Woman of 21 Mitral valve disease Left heart catheterization revealed a diastolic pressure gradient (mitral stenosis) and a moderate systolic elevation (mitral insufficiency) across the mitral valve. Crescendo systolic murmur over apex The existence of a third and fourth sound suggests that the stenosis is not dynamically significant

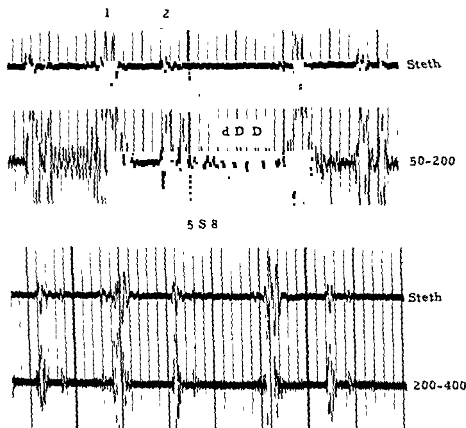


FIG 11 —(A) Woman of 54. Mitral stenosis (left heart catheterization) Accentuated first heart sound with both low and high frequency components The latter impart to the sound a ringing characteristic There is an *opening snap* of the mitral valve (KD) and a diastolic rumble of low pitch having the maximum amplitude in the frequency band 50-200

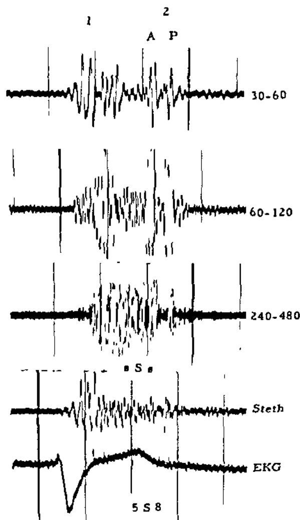


FIG 9.—Man of 23 Organic mitral insufficiency, RBBB and nodal rhythm All systolic murmur with predominance of high-frequency components which have a *diamond-shaped appearance* *Widely split* second sound Minimal early diastolic murmur transmitted from the aortic area

stenosis It is typical of mitral insufficiency if recorded at the apex by using a medium-high or high frequency band (Leatham; FIG. 10)

Basal Diastolic Murmurs

1. *Prolongation of the second aortic or pulmonic sound.* The second sound is made of three or four vibrations in decrescendo. It is typical of slight aortic or pulmonic insufficiency, which may be connected with *hypertension of the* respective circulation (FIG 7).

2. *Long diastolic murmur,* typical of advanced *aortic or* pulmonic insufficiency. In most cases, the murmur starts immediately after the second sound and gradually decreases in intensity (*murmur in decrescendo*) during mid-diastole If the vibrations are regular, there is a "sea-gull" or "dove-coo" type of murmur, *which is more common in, but not* exclusive of, an everted aortic valve. In spite of the clinical impression of decrescendo, the murmur *often has a crescendo-decrescendo* appearance in the phonocardiogram. The maximum amplitude takes place during the phase of rapid filling (FIGS 8, 9, 12 AND 13).

Apical Diastolic Murmurs

The murmur may be loudest over the mid-precordium and should be called "rumble" on account of the predominance of low-frequency vibrations.

1 *Diastolic rumble* Following the second sound, there is a short pause of silence, then an *opening snap* of the mitral valve (FIGS. 7 AND 11A) This vibration is immediately followed by a variable number of irregular vibrations. These may be only three or four, or may continue throughout diastole, increase in presystole, and continue until the following first sound One or two larger vibrations may correspond to the peak of the wave of rapid filling and be the equivalent of the third sound.

2 *Presystolic murmur.* It corresponds to that short phase of diastole preceding the first sound during which atrial contraction occurs. It is frequently a *murmur in crescendo* and its vibrations *continue with those of the first sound.* The murmur usually starts before the QRS wave of the ECG but most of it occurs during *early electric systole on account of a delay* of the first sound. The murmur includes vibrations of various frequencies with predominance of the low-pitched (FIG 11B)

Continuous Murmur

This type of murmur is typical of shunts between vessels It frequently has the auditory type of a *machinery murmur* and is found in patent ductus arteriosus and arteriovenous fistulas The murmur does not coincide exactly with the cardiac phases; it is usually *loudest at the end of systole, covers the second sound and then decreases in diastole.* The frequency of the vibrations varies, and several bands are usually

clinical difficulties Some examples will be listed below.

1 The curve of sensitivity of the human ear is such that sounds of increasing frequencies and with the same magnitude are heard as louder and louder sounds. This fact is easily revealed by phonocardiography which records the natural magnitude of the vibrations The high sensitivity of the ear for high-pitched sounds, and its poor sensitivity for low-pitched sounds are revealed by one case observed in this laboratory.

Following a myocardial infarct, a patient developed an apical systolic murmur which seemed loud After a few days, a dull diastolic rumble was also noted, creating a puzzling problem A phonocardiogram revealed the existence of a faint apical systolic murmur (relative mitral insufficiency) and a quadruple rhythm, two diastolic sounds of great magnitude and low pitch gave the impression of a diastolic rumble

2. Three phenomena, which may occur in presystole, are sometimes confused on auscultation· the *atrial type of triple rhythm (gallop)*, the *presystolic murmur* of mitral stenosis and a *crescendo-type of the first sound* (usually an innocent aberration of the normal shape). Phonocardiographic tracings reveal the exact nature of the phenomenon without difficulty

3. Clinical auscultation may reveal an abnormal sound in early diastole, the nature of which may not be clear. Phonocardiography will then reveal an opening snap of the mitral valve, a loud third sound (ventricular type of triple rhythm or gallop) or even *a short diastolic rumble*

4 Another possible error is represented by the *systolic snap* Difficulty in the clinical timing of the second sound may lead to diagnosis of mitral stenosis: The systolic snap is considered as a second sound while the second sound is considered as an opening snap of the mitral valve. Phonocardiography reveals the nature of the phenomenon

5 From time to time, clinical observers are baffled by an apparent *presystolic murmur* (an obvious impossibility) in cases with mitral stenosis and atrial fibrillation Whenever there is a short diastole, the diastolic rumble becomes tumultuous and ends with the first sound of the following cycle. The ear will register a "presystolic" murmur.

6. Whenever there is *severe tachycardia*, systole and diastole may have the same duration. It may be difficult to decide, on auscultation, whether a soft, blowing murmur is systolic or diastolic. Phonocardiography reveals the phase of the murmur without difficulty.

Functional Murmurs

The term "functional" murmur was employed about a century ago in order to separate murmurs not caused by obvious valvular deformity from the others. The most common instances were systolic murmurs of the apex or base of the heart encountered in severe anemia, pregnancy, or congestive failure, which subsequently disappeared.

In the last 30 years, some of the mechanisms causing "functional" murmurs have been clarified and can be summarized as follows:

Systolic Murmurs

1. *Severe tachycardia* may cause a moderately loud murmur. Mechanism: probably multiple (acceleration of flow, incomplete valvular closure, etc)

2. *Severe anemia* may cause a loud apical or midprecordial murmur. Mechanism. probably multiple including dilatation of the tricuspid and mitral rings (relative tricuspid and mitral insufficiency).

3 Conditions associated with increased blood volume (pregnancy), greater rapidity or quantity of systemic or sectional blood flow (hyperthyroidism, septal defects), or dilatation of one of the large arteries (aortitis, congenital dilatation of the pulmonary artery) frequently present a systolic murmur at the base Mechanism: disproportion between normal ostium and dilated vessel; trigonoidation of the valve (relative aortic or pulmonic stenosis)

4. *Acute rheumatic carditis* may cause a systolic apical murmur through congestion or edema of the mitral papillary muscles. This would lead either to tension and vibration (musical murmur) or reversible shortening, a cause of valvular insufficiency (soft blowing murmur). It also may cause a basal systolic

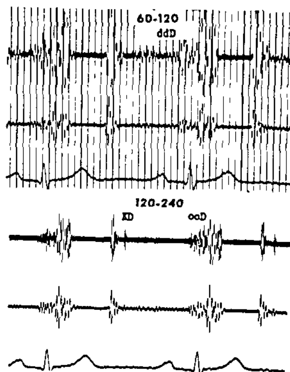


FIG 11 —(B) Woman of 35 Mitral Stenosis (*From above*) The first and fourth tracings are filtered tracings, the second and fifth tracings are stethoscopic, the third and sixth are electrocardiograms Diastolic-presystolic murmur (ddD) and opening snap (KD) Tracings recorded with a new phono system

represented, as proven by the use of different filters.

Other continuous murmurs include the "thyroid murmur" of Graves disease, the "venous hum" of the neck, the murmur of a ruptured sinus of Valsalva, the murmur of the aneurysm of a coronary artery opening into the coronary sinus, occasionally the murmur of the common arterial trunk, the murmur which develops after a Blalock-Taussig or Potts operation and that which has been recorded in stenosis of the peripheral branches of the pulmonary artery and in anomalous subclavian arteries. Arterial murmurs should be considered too, among them are the murmur of collateral intercostal arteries (coarctation of aorta) and the murmur of arteries of the breast (pregnancy).

FRICTION RUBS

Pericardial friction rubs are revealed by the tracing as high-frequency vibrations. They are often grouped in three phases· presystole, mid-systole and early diastole.[4] However, only two groups are often recorded. in systole and presystole. Differentiation of rubs from murmurs is possible if no murmurs are present. On the other hand, if murmurs and rubs are both present, graphic differentiation is near to impossible. The presystolic rub usually ends before the first sound and thus cannot be confused with a mitral presystolic murmur.[7a]

PITFALLS OF AUSCULTATION

Several pitfalls of auscultation are due to either physiologic inadequacies or unavoidable

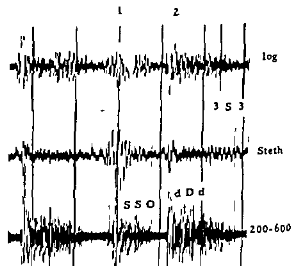


FIG 12 —Man of 46 with rheumatic aortic insufficiency and minimal stenosis Crescendo-decrescendo early-diastolic murmur in the high-frequency band Early systolic murmur

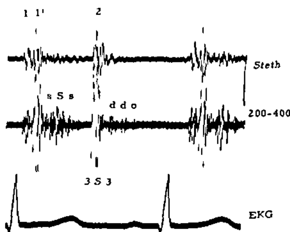


FIG 13 —Child of 8 with aortic stenosis and insufficiency (rheumatic) Diamond-shaped systolic murmur and minor diastolic murmur in decrescendo. Large ejection vibration within the first sound

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murmur through dilatation of the pulmonary artery

The phonocardiogram may be of some value in differential diagnosis because it can reveal the following possibilities: (a) The vibrations of the murmur are extremely small, whatever the cause, the murmur is insignificant. (b) The shape of the murmur reveals whether it is originating in one of the basal ostia (diamond-shaped) or in one of the A-V valves (decrescendo murmur).

Innocent murmurs are often extremely small when recorded by the phonocardiograph. It has been stated that they have a regular appearance (expression of their "groaning" or "musical" character) and that they are midsystolic or at least widely separated from the second sound (FIG 14).[87] However, these statements cannot be proven until many years have elapsed from the time of observation.

Diastolic Murmurs

It has been known for a long time that patients with a normal mitral orifice may present a low-pitched diastolic or presystolic murmur which is indistinguishable on auscultation from that of mitral stenosis Such a murmur has been described in aortic regurgitation, pericardial or hypertensive heart disease, rheumatic heart disease without mitral stenosis and myocarditis

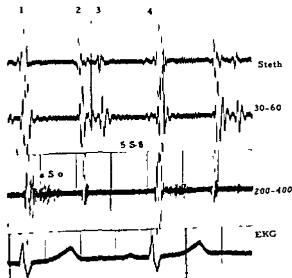


FIG 14.—Child of 8 with "innocent" pulmonic murmur. The murmur is musical and is revealed best in the medium frequency range There is a large third sound and normal fourth sound

Later on, phonocardiographic studies gave objective evidence of the existence and subsequent disappearance of the murmurs.[16, 21] In some of the cases, the murmur was documented during life by the tracing, and autopsy disclosed that no mitral stenosis existed. In some of them, the tracing demonstrated that the diagnosis of mitral stenosis was due to an auscultatory illusion (diastolic extra sounds or crescendo type of the first heart sound) while, in the others, the tracings did not reveal the "functional" nature of the murmur, and only the subsequent clinical course plus additional tracings proved that there was no mitral stenosis Other graphic studies revealed a similar murmur in patent ductus arteriosus, rheumatic or congenital heart disease or cases with an Austin Flint murmur.

In a further study, certain positive data were found helpful in recognizing the "functional" nature of the murmur. in contrast with the murmur of mitral stenosis, this murmur is frequently made of large vibrations and occurs in mid or late diastole, it is often recorded over a large area of the chest, there frequently is a third sound Certain *negative data* were also found helpful, there is no opening snap and the main vibration of the first sound has a normal relationship with the QRS complex (no prolongation of Q-1).[21 27a]

The murmur of these cases seems to be caused by a relative stenosis of the mitral valve or of both mitral and tricuspid valves (disproportion between normal ostium and large ventricle creating eddies within the ventricle) The large area of recording can be explained by the large area of contact with the precordium of the left ventricle (coronary and hypertensive cases), or the right (congenital heart disease), or both (acute carditis)

SPECIAL APPLICATIONS OF PHONOCARDIOGRAPHY

Fetal Phonocardiogram

The first tracing of fetal sounds was recorded by Pestalozza in 1891. Since then, many researchers have published fetal tracings with a gradually improving technic.

The method of fetal phonocardiography is

relatively simple and far easier than fetal electrocardiography. It permits evaluation of the rate of the fetal heart and even prenatal appreciation of severe malformations of the heart.

A microphone with a large chest piece is applied over that part of the maternal abdomen where auscultation reveals fetal heart tones. Simultaneously with the fetal sound tracing, a maternal electrocardiogram is recorded Comparison of the two proves whether or not the sounds recorded were fetal heart tones

Esophageal Phonocardiogram

Interest in this method lies in the fact that the heart sounds are collected from inside the chest, their origin is near the cardiac chambers and their transmission is not altered by bony structures. Thus, the fourth (atrial) sound takes place earlier than at the apex and may be due to the atrial contraction itself and not to its effect The phonocardiogram is recorded by using a stomach tube closed at its end, similar to that employed for recording mechanical pulsations through the esophagus The most interesting tracing is that obtained at the atrial level There, atrial sounds and mitral murmurs are more distinctly recorded than from the surface of the chest. In general, sounds and murmurs have lower frequencies than when recorded by conventional technic The heart sounds are shorter in duration

Tracheal Phonocardiogram

Tracheal phonocardiograms have been recorded in patients having a tracheal fistula. The technic consists of connecting the outer end of the tracheal cannula with a microphone by means of a short piece of rubber tube. The heart sounds are shorter and have vibrations of a lower frequency than when recorded from outside the chest

Intracardiac Phonocardiogram

Intracardiac phonocardiography was first attempted by Soulié in 1954[38] with a tiny piezo-electric microphone applied to the tip of a catheter. A second attempt was made by Yamakawa et al[39] who used a small metal stick attached to the tip of a catheter and placed in an electric circuit which used the body as a pole A third attempt was presented by Lewis et al. in 1956[19] who used a hollow cylinder of piezo-electric ceramic at the catheter tip for picking up the sound vibrations.

All the above technics require special catheters and are of difficult routine application on account of several practical disadvantages.

A new, simpler method is made possible by the use of filters and was described by our group in 1957.[23,26]

The catheter placed in one of the cardiac chambers or in the large vessels contains a column of fluid which reaches from the heart to a strain gauge or electromanometer As water is a good conductor of sound vibrations, it is possible to pick up these vibrations from the end of a catheter instead of its tip Recording is obtained by the use of three circuits of differentiation which modify the output of the strain gauge Signals having frequencies higher than 100 per second pass undifferentiated but are amplified The output of the "differentiator" increases linearly with increasing frequency up to 100 cps, then gradually flattens off to give constant output The final output is obtained through the use of a band pass filter This causes the signals to decrease at a rate of 12 decibels per octave at frequencies respectively below or above those selected by the switch while the desired frequencies pass without attenuation Bands of 60 to 120, 60 to 250 and 60 to 500 are alternatively used Simultaneous pressure and sound tracings are recorded

Following in vitro experiments, where the water of an open container was made to vibrate, sounds were recorded from the strain gauge while only minimal changes in pressure took place. Several controls were then made in animals. The following data were observed

1 Sounds and murmurs are easily recorded from inside the heart. A minimal delay of the intracardiac heart sounds (0 01 to 0 04 second) seems to occur in relationship with those recorded over the chest. However, this delay is greater for the right than for the left heart, greater for the first than for the second sound Therefore, it is due to physiologic and not to technical causes (slight asynchronism between valvular closure; recording within the heart limited to closure of one valve, recording on the chest of the sound caused by another valve).

2 The magnitude of the two main heart sounds decreases in the following order: left

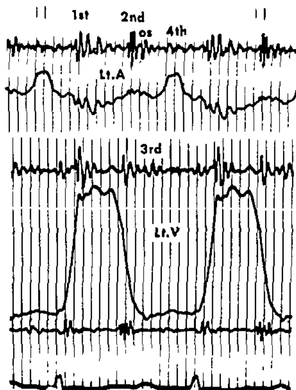


FIG 15 —Pressure tracing and intracardiac phonocardiogram recorded from the left ventricle and left atrium of a normal adult OS indicates a physiologic opening sound of the mitral valve

ventricle, right ventricle, ascending aorta and pulmonary artery, left atrium, right atrium

3. Diastolic extra sounds and systolic or diastolic murmurs are well recorded

4 Respiration does not interfere with intracardiac phonocardiography

5. The sound vibrations are poorly transmitted from one chamber to another.

6. The thin polyethylene catheter used in left heart catheterization has a slight damping effect which, however, does not prevent obtaining a good tracing (FIG 15)

The heart sounds from inside the heart can be checked before recording by using either an oscilloscope (visual) or an audiophone (auditory).

With this technic, the only new device added to the instrumentation is a specially built phonocardiographic circuit, connected by a short cable to that of the strain gauge It is self understood that, as in routine phonocardiography, a correct tracing can be obtained only by using photographic recording.

Intracardiac phonocardiograms from the left atrium, left ventricle and aorta have been studied in cases with rheumatic heart disease.[29] Several interesting data have been observed, and definite diagnostic points may be revealed by this method In general, the murmur of mitral insufficiency is larger in the left atrium; that of mitral stenosis, in the left ventricle; that of aortic stenosis, in the aorta (FIGS 16-18).

SOUND TRACINGS OF PERIPHERAL VESSELS

History While the peripheral arteries of normal subjects present no sounds (if they are not compressed), auscultation of the carotid and subclavian arteries reveals transmission of the heart sounds Compression of an artery causes the appearance of sounds or blowing murmurs, a fact which has been used for recording blood pressure (Korotkow method) Arterial sounds may be present in abnormal conditions over peripheral arteries or veins Sound tracings of peripheral arteries have been taken in order to obtain a graphic record of blood pressure or of special sound phenomena

Technic The sound tracing from the arteries of the neck can be recorded by applying over the carotid or subclavian artery a microphone provided with a medium-sized funnel and held in place by a rubber strap A sound tracing from the veins of the neck can also be obtained by a suction cup connected to a linear and a stethoscopic microphone Two simultaneous tracings of sounds and pulsations are then obtained

A sound tracing from the arteries of the limbs can be obtained by using the apparatus described by Rappaport and Luisada A double cuff is wrapped around the limb The lower cuff is inflated to the desired pressure level after switching to "register." Simultaneous pulse and sound tracings are then obtained through a "linear" and a "stethoscopic" microphone

Analysis of the waves Two sounds are generally recorded over the arteries of the neck The first of them occurs at the time of the rise of the pulse; the second, at the time of the incisura. The first sound has several vibrations and is frequently divided into two groups: The first group slightly precedes the rise of the pulse and is due to transmission of the first part of the

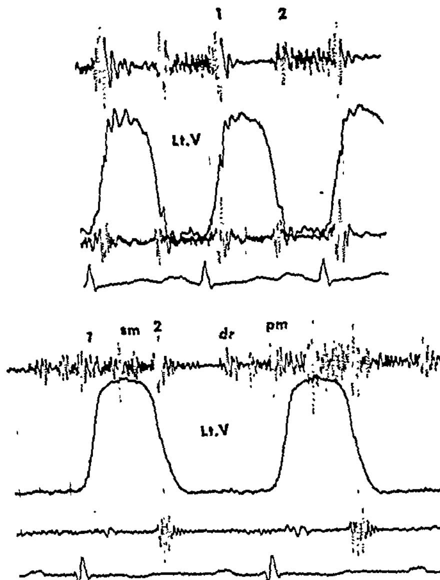


FIG 16 —Left ventricular pressure tracing and intracardiac phonocardiogram in two cases of mitral stenosis Note the diastolic-presystolic murmurs In the case below, there is also a systolic murmur

first heart sound, the second group coincides with the maximum dilatation of the vessel and is of local origin. The second sound is the result of the sudden changes of pressure which occur in the artery at the time of the incisura

The sounds recorded over the veins of the neck are usually three The presystolic sound is the largest and is made of several vibrations. It may be due to transmission of the fourth sound of the heart through the upper mediastinum, but distention of the vein in presystole is likely to be an important contributory factor The sound coinciding with the C wave is probably of local origin The third vibration is largely a transmission of the second heart sound

Normal peripheral arteries reveal only one sound, e g , a multiple vibration at the time of maximal dilatation This sound becomes weaker and simpler in the more distal vessels. More than one sound can be recorded, on the other hand, in clinical conditions such as aortic insufficiency

Records of sounds and murmurs from the

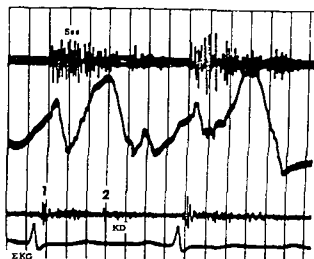


FIG 17 —Case of mitral insufficiency (*From above*) Intracardiac phono of left atrium, pressure of left atrium, external phono, ECG Note the large systolic murmur (phono) The tracing on the top is at 50 mm. of film speed, that on the bottom, at 100 mm

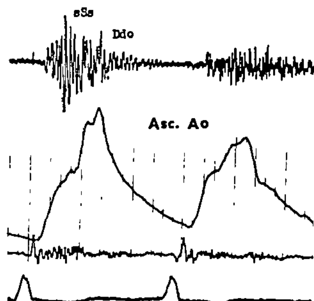


FIG 18 —Case of aortic stenosis (and minimal insufficiency) Intraaortic phonocardiogram (*above*) and pressure pulse Note the diamond-shaped systolic murmur and the short diastolic murmur

peripheral arteries and veins are not part of the regular study of a cardiac patient They may be used in individual cases either to obtain graphic evidence of unusual auscultatory phenomena or for research It should be kept in mind that, occasionally, sounds and murmurs originating in the heart are recorded best in the neck, especially in obese and emphysematous patients

NOTATIONS IN PHONOCARDIOGRAPHY

Filters

According to a recent international agreement, notation of the type and slope of the filter used should be made, as follows.

1. When only high-pass filters are used, the *first number denotes the frequency at which* the increase in amplitude reaches 10 per cent or −20 decibels of the maximum value. The slope of this point will be indicated by a second number, separated by a line (/), in decibels per octave.

Example 140(−20 db)/24

2. When band-pass filters are used, the slope of the frequency characteristic will be similarly determined, both for the high- and low-pass filters by adding a number, separated from the first by a line.

Example 140(−20 db)/24 − 500(−20 db)24

It has been agreed that these data are relevant only if the over-all frequency response given by microphone, amplifiers and recording units, is linear

Another suggestion is that the characteristics of the filters are indicated by a graph on logarithmic paper

It is understood that this sort of indication cannot take into consideration the acoustic properties of the chest even though it is supposed that a homogeneous, proportional transmission occurs, based on the physical law of "the square root of amplitude"

Location

In regard to the place where a phonocardiogram is taken, a certain agreement has been already reached following suggestions by Duchosal The data can be simplified as follows:

One should note the intercostal space, site (right = D; left = S), and the number of centimeters from the marginal line of the sternum.

Examples 2D5, 2S3, 4S5

Heart Sounds or Tones

There is no discussion of the fact that heart sounds which can be recorded even in normal subjects may be four. These should be marked with the Arabic numerals 1, 2, 3, 4.

The *first* sound is occasionally divided in two groups of vibrations. The latter will be marked as 1' and 1". The reason for this purely descriptive and noninterpretative notation is that there is still some disagreement about the mechanism of production of the various vibrations. If the first sound is composed of four or five large vibrations, the latter should not be marked, for the time being, even though the author has suggested a definite interpretation for their meaning and thus the possibility of a clear-cut notation *

The *second sound*, which is marked by the symbol 2, is often divided in two groups of vibrations There is general agreement that, both in normal subjects and in most clinical cases, the first group corresponds to closure of the aortic valve and the second group to closure of the pulmonic valve (an exception is represented by rare cases of "paradoxical splitting") Therefore, the two groups of vibrations will be marked as 2A and 2P If a paradoxical splitting occurs, an inversion of this symbol would be appropriate (2P and 2A).

The most common *diastolic sounds* are the third or fourth, or both These sounds may be unduly increased in intensity in clinical cases causing the so-called triple and quadruple rhythms (or gallop rhythms) As the latter represents merely an accentuation of the former (with possible changes of frequency), both the physiologic and pathologic third and fourth sound will be marked as 3 and 4

In the rare cases with a double third or double fourth sound, the designation will be 3' and 3" and 4' and 4" If there is a summation type of triple rhythm, this will be marked as 3-4

Snaps and Clicks

Snaps and clicks will be marked with the letter K. The opening snap of the mitral valve will be called KD (diastolic snap), as it is practically the only diastolic click or snap which can be observed

* The author suggested the letters MTPA for the four vibrations composing the first sound which are recorded in the band 60/120 and which he considered connected with four valvular events

Systolic snaps or clicks will be marked as KS, whatever the phase of systole in which they fall The so-called "ejection sound" of the aortic or pulmonary artery can also be marked KS, unless the author is convinced that this snap corresponds to the second group of vibrations of the 1st sound, in which case it would be marked as 1".

Murmurs

Murmurs may occur in either systole or diastole. Systolic murmurs will be called SSS while diastolic murmurs will be called DDD

In order to be able to mark, not only the phase of a murmur, but also its shape (diamond-shaped, decrescendo, crescendo), it is suggested to use small and capital letters and to put a small zero wherever the murmur is absent or indistinct. The following are the resulting notations.

systolic murmur in decrescendo	= Sso or Sss
continuous systolic murmur	= SSS
systolic murmur in crescendo	= sSS or ooS or osS
diamond-shaped systolic murmur	= sSs
early diastolic murmur in decrescendo	= Ddd or Ddo or Doo
early diastolic murmur which is diamond-shaped	= oDo or oDd
presystolic murmur	= odD or ooD
continuous murmur	= sSDd
friction rubs	= FF, whether in systole or diastole

Frequency-Amplitude

No notation is contemplated for the time being for these two variables of the sound vibrations. It is obvious that the degree of amplification and the type of filter greatly affect these variables The suggestions adopted at the Third World Congress will be of value in considering the frequency range of a murmur. Notation of the degree of amplification should await further work on calibration

"Phonocardiogram"

Phonocardiogram originates from Greek words meaning "sound," "heart" and "graph". The abbreviation of the term is PKG.

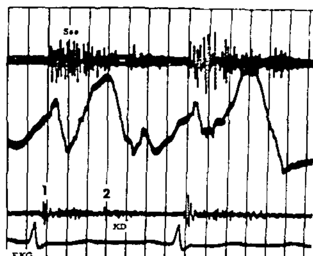


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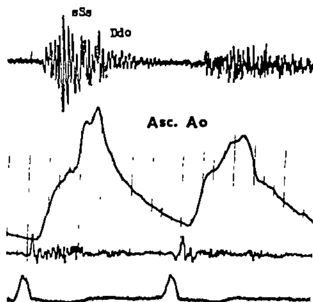


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1 When only high-pass filters are used, the first number denotes the frequency at which the increase in amplitude reaches 10 per cent, or −20 decibels of the maximum value. The slope of this point will be indicated by a second number, separated by a line (/), in decibels per octave

Example 140(−20 db)/24

2 When band-pass filters are used, the slope of the frequency characteristic will be similarly determined, both for the high- and low-pass filters by adding a number, separated from the first by a line

Example 140(−20 db)/24 − 500(−20 db)24

It has been agreed that these data are relevant only if the over-all frequency response, given by microphone, amplifiers and recording units, is linear

Another suggestion is that the characteristics of the filters are indicated by a graph on logarithmic paper.

It is understood that this sort of indication cannot take into consideration the acoustic properties of the chest even though it is supposed that a homogeneous, proportional transmission occurs, based on the physical law of "the square root of amplitude."

Location

In regard to the place where a phonocardiogram is taken, a certain agreement has been already reached following suggestions by Duchosal. The data can be simplified as follows:

One should note the intercostal space, site (right = D, left = S), and the number of centimeters from the marginal line of the sternum

Examples 2D5, 2S3, 4S5

Heart Sounds or Tones

There is no discussion of the fact that heart sounds which can be recorded even in normal subjects may be four. These should be marked with the Arabic numerals 1, 2, 3, 4.

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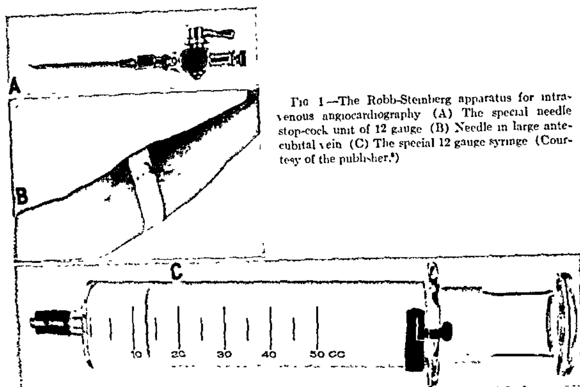


FIG 1—The Robb-Steinberg apparatus for intravenous angiocardiography (A) The special needle stop-cock unit of 12 gauge (B) Needle in large antecubital vein (C) The special 12 gauge syringe (Courtesy of the publisher.[8])

trizoate (Urokon) 70 per cent is a highly satisfactory agent Despite inability of predicting reactions by pretesting (intradermal, intraoral, opthalmic and intravenous tests), the number of untoward reactions remains remarkably small Recent observations have also shown that a calm, confident and nonapprehensive attitude during injection, with care not to alarm the patient, still further reduces reactions In many centers, experience with large numbers of cases has shown that preliminary medication to allay emotional stress and the administration of antihistamines are unnecessary. Anesthesia, unless the patient is uncooperative, should be avoided because such agents by themselves are hazardous Although uncommon, reactions such as *hypotension*, syncope, shock, apnea, pulmonary edema, cardiac arrest, fever and convulsions still occur; fatalities, however are rare These reactions are probably due to drug idiosyncrasy and may be minimized by exercising good judgment in the selection of the case for angiocardiography. The high-risk patients (cyanotic heart disease cases) should be studied only in the hospital where special facilities and skills are available. *If cardiac arrest occurs, open thoracotomy* and cardiac massage followed by proper respiration and surgical closure of the chest may be lifesaving Search for the ideal, safe and nonreactive contrast substance must continue [7]

Intravenous angiocardiography, like right heart catheterization, because of the complexity of some types of heart disease, cannot be expected to be suitable for all types of disease of the cardiovascular system Accordingly, selective angiography by needle and catheter injection, particularly for the demonstration of valvular deformities and certain types of shunts, may be necessary. Like all new special procedures, their indications need to be evaluated However, it seems unlikely that these technics will displace intravenous angiocardiography.

The Normal Cardiac Silhouette

Utilizing the experience gained from visualizing the cardiovascular structures angiocardiographically, the idealized cardiac silhouette in the normal can be ascertained (FIG. 3).[3] These also serve admirably as a guide for roentgen recognition of the various *cardio-*

— 7 —

Practical Roentgen Physiology of the Cardiovascular System

By ISRAEL STEINBERG, M D

Associate Clinical Professor of Medicine and Radiology, Cornell University Medical College, Assistant Radiologist and Physician, New York Hospital, New York, New York

ROENTGEN'S epochal discovery of the x-rays in 1895 began a new era in the study of cardiovascular anatomy and dynamics during life For the first time, the heart and great blood vessels became truly visible The solid blood-containing heart, surrounded by translucent lungs made the cardiac silhouette discernible Rotation of the patient aided recognition of individual heart chambers, but even then an incomplete picture of the cardiovascular anatomy resulted because the cardiac chambers were seen fluoroscopically and roentgenographically as a single homogeneous mass, while the great vessels were usually indistinct, incomplete or not seen at all Recognition of valvular calcification of the aortic and mitral valves also aided the diagnosis of valvular disease (stenosis) Complete delineation of the cardiac chambers and great blood vessels was achieved by contrast visualization of the cardiovascular structures, now known as angiocardiography

Physiology of Intravenous Angiocardiography

The practical method of visualizing the four cardiac chambers and great vessels was reported by Robb and Steinberg in 1938, and published in January, 1939, over 21 years ago[18] Nowadays, when there is a growing tendency to insert needles and introduce catheters into the heart and great vessels, it may seem archaic to discuss the method of intravenous angiocardiography.

Failure to visualize completely the cardiovascular system by intravenous angiocardiography occurs because the technic requires meticulous attention to a few details which, incidentally, have remained unchanged during the twenty year period A large special bore (12 gauge) needle-stopcock unit and syringe are necessary for rapid injection (Fig 1). Speed of injection is essential if the contrast medium is to be delivered into the heart as a bolus. Moderate inspiration during injection aids in sucking the contrast material into the thorax; keeping the patient from inadvertently performing the Valsalva maneuver prevents delay of passage of the medium into the superior vena cava (Fig 2) In cooperative adults, the erect position with thorax against cassette minimizes the possibility of the cardiovascular structures being obscured by the thoracic bony cage and diaphragm[3]

Advances in rapid serial roentgenography (multiple exposures of film per second and cineangiocardiography with the image amplifier) have made unnecessary preliminary circulation time determinations in patients without heart failure and/or valvular heart disease Roentgen exposures of 5 seconds in infants and a duration of 8 to 10 seconds in adults are all that are needed for a complete study of the passage of contrast material from the arm into the thoracic aorta In heart failure and in patients with valvular heart disease (especially mitral valvular disease), a modified circulation time evidenced by a bitter taste can be determined by rapidly injecting 3 cc sodium decholin mixed with 15 cc normal saline via the Robb-Steinberg needle. In patients with a prolonged circulation time, multiple exposures per second are unnecessary because the slowed circulation results in good visualization of the cardiovascular system Roentgenograms made at 1 second intervals for the duration of the circulation time have proved very satisfactory.

Improvements in the concentrated organic iodide contrast materials have reduced reactions during angiocardiography Sodium ace-

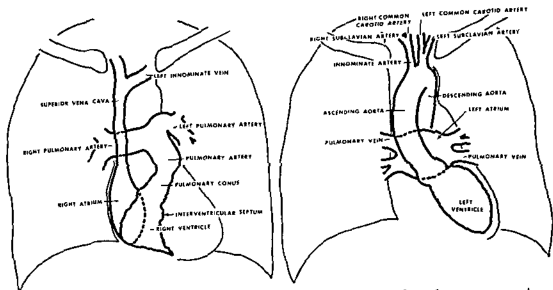


FIG 3—The "idealized" angiocardiogram in various positions—a guide to fluoroscopic, roentgen and angiocardiographic interpretation (A) *Left* Frontal right heart study (B) *Right.* Frontal left heart study

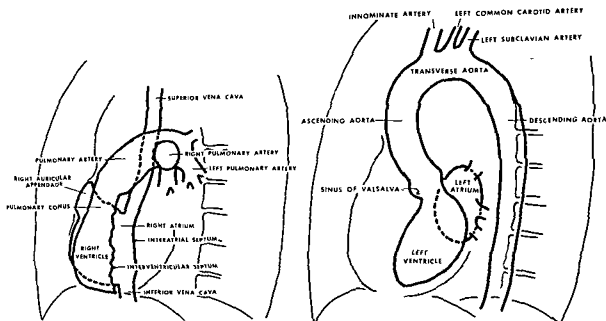


FIG 3—(C) *Left* Left anterior oblique projection of the right side of the heart (D) *Right* Left anterior oblique projection of the left heart

important in the differential diagnosis (FIG 5)[3] Similarly, aneurysms with thrombi may not pulsate (FIGS 6–9)[22]

Angiocardiographic Physiology of Congenital Heart Disease

Pulmonary stenosis There are two main types of pulmonary stenosis, valvular and infundibular The valvular (FIG 10) consists of a dome-shaped membranous structure (opened umbrella-like) formed by the fused pulmonary cusps. An orifice, usually centrally located, can be identified by a "jet" of opacified blood The valve cusps are mobile despite fusion and are easily recognized, especially during diastole The right ventricle is enlarged, and during diastole thickening and trabeculation of the wall can be seen The outflow tract of the



FIG 2—Effects of the Valsalva Maneuver Angiocardiogram of a patient with rheumatic mitral stenosis who performed the Valsalva maneuver during injection of contrast material via the left arm The right innominate, jugular and subclavian veins were opacified delaying filling of the right atrium (Courtesy of Dr S B Rosenbluth)

vascular structures, especially during fluoroscopy More important, they may be regarded as normal standards and serve as a basis for interpretation of diseased states.

Differentiation of Enlarged Hearts from Pericardial Effusion

Enlargement of the cardiac silhouette whether due to dilatation of the chambers of hypertrophy of the walls indicates disease of the cardiovascular system. Accordingly, in the absence of murmurs and a rheumatic history or stigmata, it is important to perform angiocardiography for differential diagnosis Pericardial effusion can usually be recognized by showing a nonopacified area surrounding the heart in frontal view (FIG 4) [24, 25] Rarely, bronchogenic pericardial cysts and primary myocardial tumors (rhabdomyomas) also cause myocardial enlargement [8]

Differentiation of Aneurysms from Mediastinal Tumors

Mediastinal tumors adjacent to cardiac chambers and great blood vessels may pulsate vigorously. Angiocardiography then becomes



Fig 4—The cardiac silhouette in pericardial effusion (A) *Left* Conventional frontal roentgenogram (B) *Right* Conventional left lateral roentgenogram



Fig 4—(C) *Left* Frontal angiocardiogram showing the normal superior vena cava (SVC), the right atrium (RA), ventricle (RV) and pulmonary artery (PA) with pericardial fluid to the right and inferiorly to these structures (D) *Right* When the left heart is opacified (left atrium [LA]), left ventricle (LV) and aorta (AO)) there is fluid to the left and inferiorly—the classical appearance of pericardial effusion (Courtesy of the publisher[26])

with tetralogy of Fallot and transposition syndromes.

Aortic stenosis Aortic stenosis may be divided into the valvular and subvalvular types In the valvular type, the cusps are thickened and may be fused to form a dome-shaped diaphragm with a central opening Frequently, there is poststenotic dilatation of the ascending aorta Clinically, it is almost impossible to distinguish between aortic valvular and subaortic types of stenosis This is also true after angiocardiography. Figure 12 shows dome-shaped deformities of the aortic cusps with poststenotic dilatation of the ascending aorta.

Congenital mitral stenosis Isolated congenital mitral stenosis is rare, but association with aortic valve, aorta and ductus arteriosus malformations is not uncommon[5] In the angiocardiogram, isolated enlargement of the left

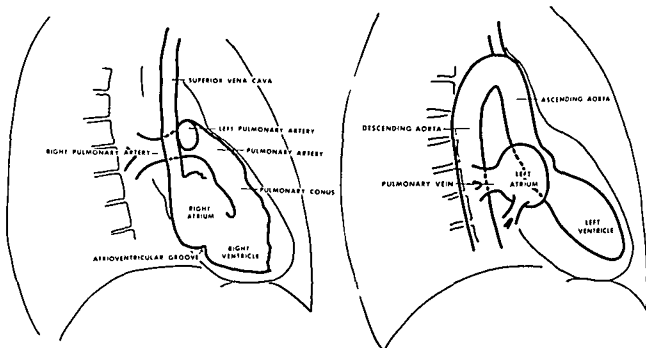


Fig 3—(E) *Left* Right anterior oblique view of the right heart (F) *Right* Right anterior oblique view of the left heart

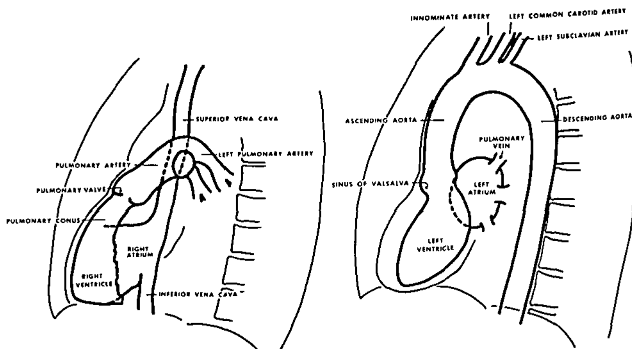


Fig 3—(G) *Left* Lateral appearance of the right heart (H) *Right* Lateral appearance of the left side of the heart (Courtesy of the publisher [a])

right ventricle is of good caliber during diastole but may appear contracted and simulate infundibular stenosis during systole. Multiple stenosis of the pulmonary arteries, chiefly the main branches, has recently been reported and called coarctation of the pulmonary arteries (Fig 11).[1] Infundibular stenosis of the pulmonary artery rarely occurs as an isolated lesion Usually, it is associated with deformities of the ventricular septum, occurring in patients

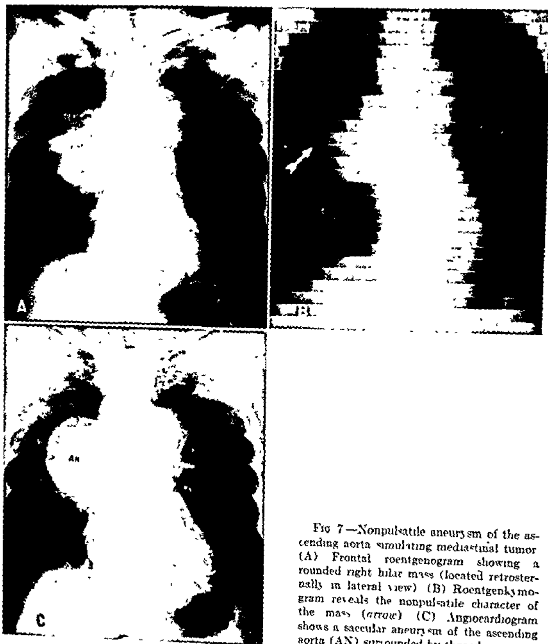


FIG 7—Nonpulsatile aneurysm of the ascending aorta simulating mediastinal tumor (A) Frontal roentgenogram showing a rounded right hilar mass (located retrosternally in lateral view) (B) Roentgenkymogram reveals the nonpulsatile character of the mass (*arrow*) (C) Angiocardiogram shows a saccular aneurysm of the ascending aorta (AN) surrounded by thrombus

subclavian arteries are often dilated, and the left common carotid artery is frequently enlarged Collateral channels, particularly the internal mammary and shoulder girdle arteries, may be dilated and tortuous The intercostal arteries are not as well visualized The exact site of coarctation is readily identified at a variable distance beyond the left subclavian artery (FIG 14) There may be an area of abrupt constriction which is obscured in part by overlapping of the poststenotic segment of the aorta The diameter of the lumen at the site of coarctation cannot be determined. Prompt filling of the aorta distal to the stenosis may occur via collaterals in the absence of any opening The length of the stub of aorta distal to the left subclavian artery and proximal to the site of stricture has varied Dilated intercostal arteries may occasionally be seen connecting with the poststenotic descending aorta Rarely, an aneurysm of the intercostal vessels can be recognized



FIG 5—Pulsatile right paratracheal mass simulating aneurysm of the aorta (A) *Left* Conventional frontal roentgenogram showing a mass (*arrow*) contiguous with the ascending aorta (B) *Right* Angiocardiogram showing the intact aorta (AO) Operation disclosed a bronchogenic cyst

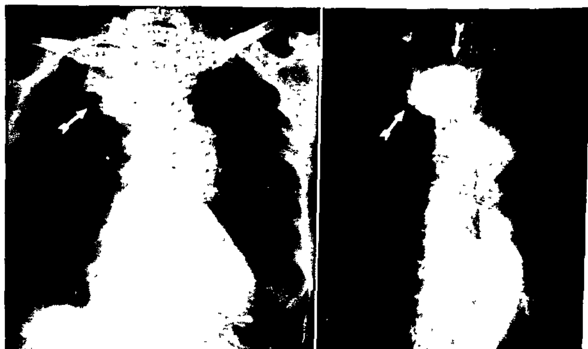


FIG 6—Nonpulsatile syphilitic aneurysm of the innominate artery (A) *Left* Conventional frontal roentgenogram showing enlargement of the heart and a large right superior mediastinal mass (*arrow*) compressing and deviating the trachea to the left (B) *Right* Angiocardiogram showing a saccular aneurysm of the innominate artery with surrounding thrombus (*arrows*)

atrium, delay in emptying and enlargement of the right ventricle and pulmonary artery are seen in uncomplicated congenital mitral stenosis (FIG 13).

Coarctation of the aorta Angiocardiography in patients with coarctation of the aorta is customarily performed in the left anterior oblique projection, this affords an open view of the aortic arch similar to exposure during an operation The angiocardiographic findings may be summarized as follows· The left ventricle may be enlarged The ascending aorta, often normal in young patients, is usually dilated in the adult The innominate and left



FIG 9—*Nonpulsatile dissecting aneurysm of the thoracic aorta* (A) *Left* Frontal conventional roentgenogram showing a hugely widened supracardiac shadow (B) *Right* The frontal angiocardiogram reveals a double-barrel aorta—the inner channel, the descending aorta, is narrowed, while the outer channel contains thrombus and contrast material (arrow)

the left side of the heart and the aorta is usually of poor quality due to dilution of the contrast agent by large volumes of shunted blood Persistent opacification of the pulmonary arteries also occurs as a result of a large ventricular septal defect, patent ductus arteriosus and defects in the aorticopulmonary septum, but the right atrium does not share in the opacification It is occasionally difficult to establish with certainty that recirculation of contrast agent is actually present A slow injection or the trapping of the contrast agent in arm or neck veins may result in prolonged filling of the right atrium and lead to a mistaken angiocardiographic diagnosis of an atrial defect

Ventricular septal defects Angiocardiography may show no abnormality in the presence of small defects in the ventricular septum There may be evidence of reopacification of the right ventricle (but not the right atrium) at the time of left heart filling, but, as is the case with atrial defects, the finding is difficult to evaluate In high ventricular septal defects, there may be angiocardiographic demonstration of shunting of blood in both directions across the defect, especially with pulmonary hypertension (FIG 16) Even after cardiac catheterization it may be difficult to distinguish between such a lesion and the Eisenmenger complex

Patent ductus arteriosus The angiocardiographic findings which have been observed in patients with patent ductus arteriosus include, (1) dilatation of pulmonary arteries, (2) high position of the left pulmonary artery, (3) a defect in the column of contrast substance within and at the time of filling of the pulmonary artery and the left pulmonary artery caused by a "jet" of nonopacified blood issuing from the ductus (FIG 17A), (4) persistent opacification of the pulmonary arteries at the time of aortic filling (FIG 17B), (5) localized dilatation of the aorta at the site of origin of the ductus and (6) rarely, opacification of the ductus itself These signs have all been absent in patients with proved cases of patent ductus arteriosus In some patients with patent ductus arteriosus, the pulmonary arterial blood pressure may be elevated to systemic levels When this occurs, the direction of flow across the ductus becomes reversed with the production of typical clinical and angiocardiographic findings As illustrated in FIGURE 18, early opacification of the descending but not the ascending aorta occurs Later films show opacification of the ascending aorta, and this rules out the presence of stenosis of the aortic arch As would be expected, this situation results in cyanosis localized to the lower but not the upper extremities [14]

Aortic septal defect. Since the two lesions of

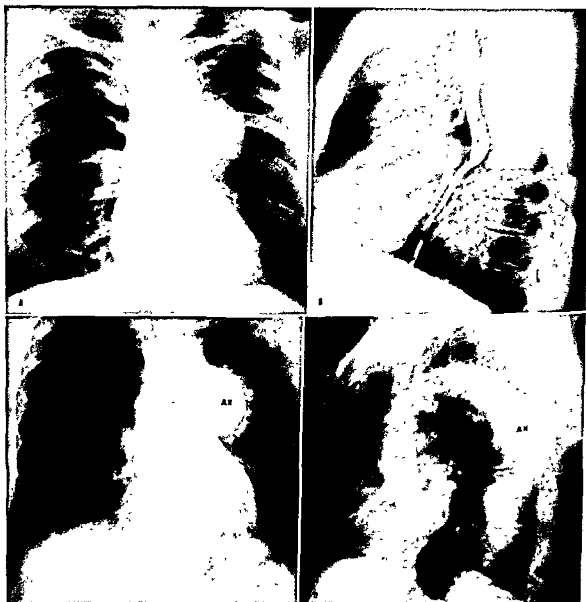


FIG 8—Nonpulsatile arteriosclerotic aneurysm of the descending aorta simulating a posterior mediastinal tumor (A) Conventional frontal roentgenogram showing a rounded left hilar mass (B) The lateral esophagram shows the mass over the spine, the lower portion of the esophagus is displaced forward (C) Frontal angiocardiogram showing the aneurysm (AN) surrounded by thrombus (D) The left anterior oblique angiocardiogram also shows the aneurysm (AN) and tortuosity of the lower part of the descending aorta which had caused the esophageal displacement

Simple Shunts

Atrial septal defects The angiocardiogram in atrial septal defects reveals right-sided heart and pulmonary arterial enlargement The contrast agent can sometimes be seen to pass from the right to the left atrium Filling defects due to left-to-right shunting of blood may be often recognized in the right atrium (FIG 15) Associated defects, such as pulmonary stenosis, tricuspid atresia and anomalous drainage of pulmonary veins frequently are accompanied by right-to-left atrial shunts. The usual finding is persistent opacification of the right atrium, right ventricle and pulmonary arteries which lasts during the entire period of cardiac filling and results from recirculation of opacified blood from the left to the right atrium Opacification of the chambers of



FIG 11—Stenosis of right pulmonary artery in a 4 year old child with pulmonic valvular stenosis Cardiac catheterization showed right ventricle pressure of 60/6, pulmonary artery (mean) 10 mm Hg There was also pressure change on withdrawal of catheter from the right pulmonary artery Stenosis (*arrow*) of the right pulmonary branch with poststenotic dilatation of the right pulmonary artery is clearly seen in the angiocardiogram

The angiocardiographic identification of pulmonary stenosis may be direct or indirect Selective angiocardiography has considerably increased the yield of direct diagnosis of pulmonary stenosis [11] In only about half the cases the pulmonary infundibular or valvular narrowing is seen with the intravenous method The presence of stenosis may, however, be inferred with reasonable assurance from one or more of the following findings (1) The peripheral pulmonary arteries are unusually small (2) They fill poorly with opaque substance (3) The central pulmonary arteries, even though fairly large and well filled, are irregularly deformed in appearance, while the peripheral branches are disproportionately small Even though good filling of apparently normal pulmonary arteries is seen, pulmonary stenosis cannot be excluded by angiocardiography (although in such cases it is reasonable to conclude that marked reduction in pulmonary blood flow is not present). Furthermore, failure of the pulmonary arteries to fill with contrast substance may be the result of transposition of the great blood vessels rather than pulmonary stenosis

Dextroposition or overriding of the aorta is manifest in the angiocardiogram by the immediate passage of contrast agent from the right ventricle to that vessel, a direct angiocardiographic demonstration of the cause of the patient's cyanosis (FIG 10) In general, the degree to which the aorta overrides can be estimated from the findings If early aortic opacification is faint as compared to the density in the pulmonary artery and as compared to that obtained later in the angiocardiographic series when contrast substance reaches the aorta from the left ventricle, it may be assumed that only slight dextroposition exists

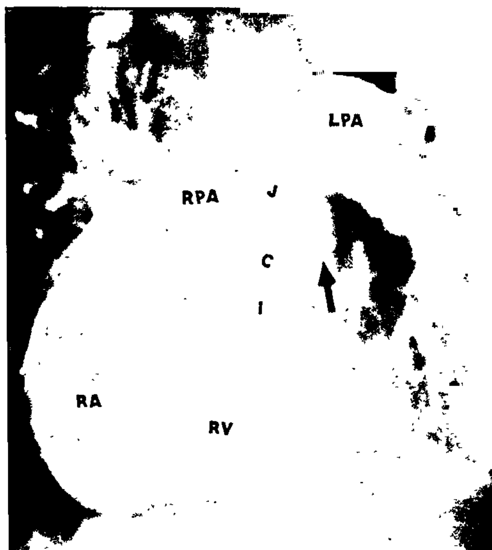


Fig 10—Pulmonary valvular stenosis in 7 year old child Frontal angiocardiogram reveals enlargement of the right atrium (RA) and ventricle (RV) Infundibulum (I) of right ventricle ends in everted pulmonary cusps (C) Adjacent is dilated sinus of Valsalva of pulmonary artery (*arrow*) "Jet" (J) can be seen through the stenotic pulmonic valve, causing poststenotic dilatation of left pulmonary artery (LPA) In contrast is normal-sized right pulmonary artery (RPA) Note enlargement of central pulmonary arterial tree but decreased blood flow through lungs (Courtesy of the publisher[27])

patent ductus arteriosus and aorticoseptal defect produce the same hemodynamic abnormality, it is usually not possible by means of angiocardiography or cardiac catheterization to distinguish between patent ductus arteriosus and defects occurring between the aorta and the pulmonary artery just above the semilunar valves Fortunately, the latter lesion is rare. The diagnosis may be suspected clinically and confirmed by thoracic aortography Such defects have been occasionally repaired.

Complex Malformations

Tetralogy of Fallot Tetralogy of Fallot consists essentially of the combination of two lesions, pulmonary stenosis (infundibular or valvular) and dextroposition or overriding of the aorta A physiologic if not an anatomic ventricular septal defect always occurs when the aorta overrides the ventricular septum, and right ventricular hypertrophy is the result of pulmonary stenosis rather than a fundamental component of the anomaly



FIG 19—Frontal angiocardiogram, showing classic coarctation and post-stenotic dilatation of aorta (*arrow*) in a 6 year old boy AO, moderately dilated ascending aorta (Courtesy of the publisher[22])

Marked enlargement of the main stem pulmonary artery and dilatation of the pulmonary and peripheral branches with dense opacification are usually present

Transposition of the great blood vessels It may be difficult to distinguish with certainty between the extreme dextroposition of the aorta associated with severe pulmonary stenosis and complete transposition of the aorta and pulmonary artery, particularly when pulmonary stenosis complicates transposition. The aorta in transposition "takes off" far anteriorly and describes an open, rounded course through the upper part of the thorax (FIG 20) The density of contrast substance within the aorta closely approximates that within the right ventricle If the pulmonary arteries appear prominent in the conventional roentgenogram or unusually pulsatile at fluoroscopy and yet fill poorly or not at all during angiocardiography, transposition of the aorta and pulmonary artery should be strongly suspected When pulmonary stenosis is present, the diagnosis may be even more difficult Although in patients with transposition of the great blood vessels life is dependent on some intercommunication between the systemic and pulmonary circuits, these shunts are rarely demonstrated by angiocardiography

Taussig-Bing syndrome In the Taussig-Bing syndrome a transposed aorta and a large pulmonary artery arise from the right ventricle; the pulmonary artery partially overrides the ventricular septum A high ventricular septal defect and right ventricular hypertrophy complete the syndrome The diagnostic angiocardiographic feature consists of simultaneous filling of the dilated pulmonary artery and aorta, differentiating it from the ordinary transposition, however, this is not pathogno-

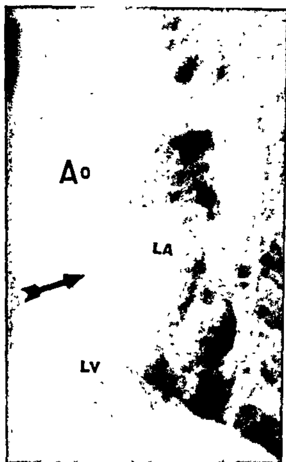


FIG 12—Angiocardiogram of 7 year old child with history of aortic murmur since birth Note deformed aortic cusps (*arrow*) and poststenotic dilatation of ascending aorta (AO) LA, left atrium, LV, left ventricle (Courtesy of the publisher[?])

Furthermore, the position of the base of the aorta with respect to the heart border and the contour of the aortic arch are of significance The farther anterior the origin of the aorta and the more rounded out its course throughout the thorax, the greater is the degree of aortic overriding The so-called pseudotruncus arteriosus is a variant of the tetralogy of Fallot in which the pulmonary artery is markedly stenotic if not atretic, circulation to the lungs being via bronchial arteries

In summary, the angiocardiographic diagnosis of tetralogy of Fallot depends on the simultaneous filling of the aorta and pulmonary artery from the right ventricle and the demonstration of pulmonary stenosis. Infundibular stenosis of the right ventricle is probably the commonest type of pulmonary deformity although the valvular or the combination of both types may occur. In most cases the main pulmonary artery is diminished in caliber, but in others it is of normal size. In severe degrees of pulmonary stenosis, the pulmonary artery is apt to be small and fills later than the opacified aorta. Poststenotic dilatation of the pulmonary artery occurs more frequently in valvular than in infundibular stenosis. The pulmonary vasculature can often best be evaluated by angiocardiography In the tetralogy of Fallot it is strikingly diminished

Angiocardiography readily demonstrates associated anomalies of the aortic arch and branches A right aortic arch and the position of the branches may be often a determining factor in the type of aorticopulmonary operation, i e, whether Pott's anastomosis or the Blalock-Taussig operation is done

Eisenmenger complex In the Eisenmenger complex, there is an overriding aorta associated with pulmonary hypertension. Angiocardiographically, the overriding aorta and pulmonary artery are often filled simultaneously from the right ventricle However, with slight degree of overriding the aorta may be only faintly filled The differential diagnosis between the Eisenmenger complex and a high ventricular septal defect is made with great difficulty even after cardiac catheterization

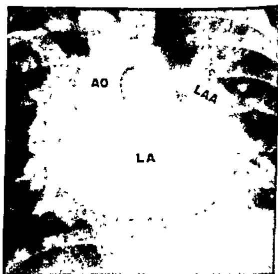


FIG 13—Congenital mitral stenosis in 21 month old boy Frontal angiocardiogram shows a markedly enlarged left atrium (LA), LAA, left atrial appendage, AO, aorta (Courtesy of the publisher[?])

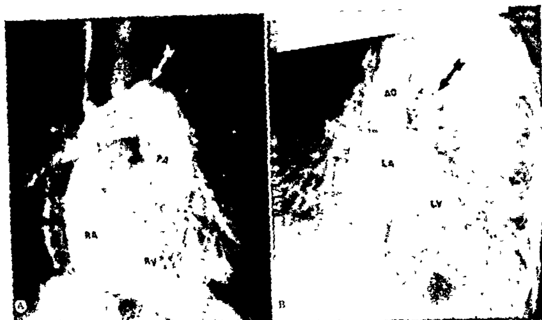


FIG 17.—Patent ductus arteriosus with "jet sign" in left pulmonary artery (A) *Frontal* angiocardiogram of 14 year old girl reveals *rounded* pinpoint *area* of nonopacification in left pulmonary artery (*arrow*) PA, pulmonary artery, RV, right ventricle, and RA, right atrium (B) When structures of left side of heart are filled (LA, left atrium, LV, left ventricle; and AO, aorta), *there is* reopacification of left pulmonary artery (*arrow*) (Courtesy of the publisher[37])



FIG 18.—Reversal of shunt in patent ductus arteriosus (A) *Left* Enlarged frontal angiocardiogram of 4 months old infant shows, filling of ductus arteriosus (*upper arrow*) and descending aorta (*lower arrow*) at time of filling of right side of heart (RA right atrium, RV, right ventricles, and PA, pulmonary artery) (B) *Right* Left anterior oblique angiocardiogram also demonstrates the reversed ductus (*arrow*) The right ventricle (RV), the pulmonary artery (PA) and the descending aorta (AO and arrow) are opacified



Fig 15—Huge atrial septal defect in 13 year old girl (A) Frontal angiocardiogram at one and one half seconds shows the superior vena cava (SVC) emptying into the left atrium (LA) Right atrium is nonopacified because of left-to-right flow through atria (B) A second later, left ventricle (LV) and aorta (AO) are opacified SVC, superior vena cava (Courtesy of the publisher[27])

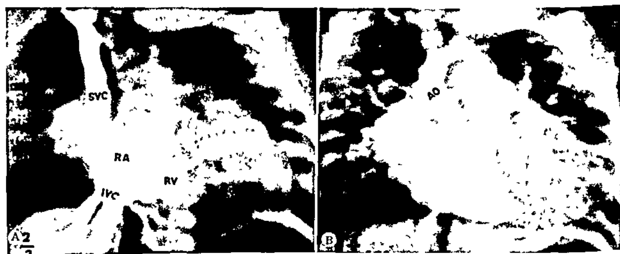


Fig 16—Ventricular septal defect in 3½ month old infant (A) Two-third second after injection, superior vena cava (SVC), right atrium (RA), inferior vena cava (IVC) and right ventricle (RV) are opacified (B) One second later, there is filling of plethoric lung vasculature and aorta (AO) At autopsy, a few days later, huge ventricular septal defect and pulmonary arteriolar sclerosis were found (Courtesy of the publisher[27])

monic, since transposition with a large ventricular septal defect can produce the same picture Outlining the ventricular septum with a clear origin of the pulmonary artery from both ventricles and transposition of the aorta are essential for diagnosis of this complex (Fig 21).

Tricuspid atresia In tricuspid atresia, blood flow is from the right atrium, across an atrial defect into the left ventricle and then into the



FIG 20—Transposed great vessels in 5 month old infant (A) Frontal angiocardiogram at 2.33 seconds shows a dextroposed aorta (AO) arising from right ventricle (RV) Enlarged right atrium (RA) and inferior vena cava (IVC) are also opacified Pulmonary artery (PA) is just beginning to fill (B) Lateral angiocardiogram at one and one-third seconds demonstrates anterior position of aorta (AO) arising from right ventricle (RV) IVC, is inferior vena cava; right atrium (RA) is also opacified (Courtesy of the publisher)



FIG 21—Taussig-Bing syndrome in 5 year old child Frontal angiocardiogram at one and one-half seconds shows simultaneous filling of huge pulmonary artery (PA) and dextrorotated aorta (AO) RV, common right ventricle, RA, right atrium, descending aorta (arrow). (Courtesy of the publisher)



FIG 19—Angiocardiogram, at 1.5 seconds, showing tetralogy of Fallot in a 4 year old child Simultaneous filling of huge right ventricle (RV) and dilated dextroposed aorta (AO) seen Arrow points to stenosis of pulmonary conus Note decreased blood flow in lungs (Courtesy of the publisher[27])

aorta and pulmonary arteries The origin of the great vessels may vary considerably Both may arise from the left ventricle, either may arise from a diminutive right ventricle which receives blood from the left ventricle via a ventricular septal defect Pulmonary stenosis may occur as may an associated patent ductus arteriosus As is illustrated in FIGURE 22 A AND B, angiocardiography usually reveals the abnormal course of blood flow clearly In this example, the aorta takes origin from a diminutive, nonfunctioning right ventricle (filled via an interventricular septal defect) while the small pulmonary arteries give evidence of pulmonary stenosis In another case reported elsewhere, tricuspid atresia was associated with dextrocardia, a common atrium, an anomalous pulmonary vein entering a left superior vena cava, a functioning single ("left") ventricle, severe pulmonary stenosis and a large patent ductus through which blood reached the lungs All the anatomic features except the tricuspid atresia itself were clearly shown in the angiocardiogram Since the presence of tricuspid stenosis or atresia may be considered highly probable when cyanosis and left axis deviation of the electrocardiogram occur together, angiocardiography need be used only when operation is contemplated or in atypical cases

Anomalies of the Large Arterial Vessels

Pulmonary artery. Idiopathic or primary dilatation (aneurysm) of the pulmonary artery is rare Angiocardiography readily demonstrates enlargement of the pulmonary artery. However, the diagnosis of primary dilatation of the pulmonary artery can be made only when the many causes of pulmonary artery dilatation, such as pulmonic stenosis, congenital heart disease (atrial and ventricular septal

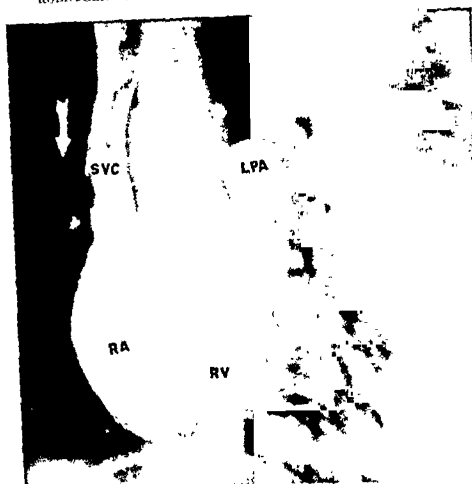


FIG 23.—Congenital absence of right pulmonary artery Frontal angiocardiogram of a 12 year old girl shows filling of right heart structures SVC, superior vena cava, RA, right atrium; RV, right ventricle, LPA, left pulmonary artery, and absent right pulmonary artery (*arrow*). (Courtesy of the publisher[27])

possible. Diagnosis of these conditions is important, the reanastomosis of pulmonary veins into the proper atrium in specially selected cases may be life-saving On the other hand, patients with partial anomalous pulmonary venous drainage complicated by a large atrial septal defect, pulmonary stenosis, or acquired rheumatic heart disease with mitral stenosis may be seriously handicapped and require operation Complete study with cardiac catheterization as well as angiocardiography is necessary for full evaluation Similarly, thorough study is indicated in patients suspected of having totally anomalous pulmonary venous drainage[19]

When anomalous pulmonary veins from the lungs or the whole left lung insert into the left innominate vein, a characteristic roentgenographic picture results The abnormal mediastinal and hilar shadows have been likened to a "figure of eight," a "dumbbell silhouette," a "mediastinal mustache" and a "cottage loaf" On angiocardiography, the widened mediastinal and hilar shadows on the left are usually related to the dilated common pulmonary venous trunk (persistent left superior vena cava) inserting into the left innominate vein, while on the right side they are due to the dilated superior vena cava enlarged because of the increased blood flow from the left innominate vein (FIG 25)[19]

Total insertion of pulmonary veins into the superior vena cava and right atrium was found in a patient along with an associated atrial septal defect. (In total anomalous pulmonary venous drainage this must exist for life) The

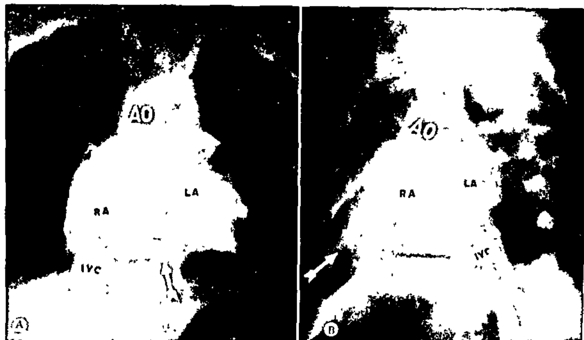


FIG 22—Tricuspid atresia in 4 month old infant (A) Angiocardiogram reveals enlarged right atrium (RA) being opacified from the inferior vena cava (IVC) Right ventricle (*arrow*) is unopacified, while left atrium (LA) is filled via atrial shunt Ascending aorta (AO) is also opacified (B) Lateral angiocardiogram shows unfilled right ventricle (*arrow*) Right atrium (RA) and left atrium (LA) are opacified via septal defect IVC is inferior vena cava, aorta (AO) is also opacified (Courtesy of the publisher [2])

defects and patent ductus arteriosus), rheumatic heart disease, cor pulmonale, heart failure and syphilis are excluded It rarely causes disability and requires no treatment

Either a right or left main branch of the *pulmonary artery may* be congenitally absent, and the diagnosis of this newly recognized entity can often be made by conventional roentgenography There is displacement of the mediastinum (mediastinal herniation), trachea and heart by an overdistended lung, while the opposite lung is hypoplastic and poorly vascularized The angiocardiographic study demonstrates the absence of a pulmonary artery with good vascularity of the overdistended lung Studies with use of rapid serial roentgenograms have disclosed that the bronchial arterial circulation is responsible for the poorly vascularized lung Experience in 3 cases indicates that absence of a main branch pulmonary artery, when uncomplicated, is usually discovered during routine chest survey The condition may be mistaken for a mediastinal tumor. This anomaly, when uncomplicated, requires no treatment, and the prognosis is good However, such patients must be kept under observation, for the occurrence of pneumonia in the normal lung may wreak havoc with the gaseous exchange processes Absence of a main branch pulmonary artery may also occur in association with cyanotic congenital heart disease (FIG 23) [20]

Aorta Aneurysms of the aortic sinuses (of Valsalva) are rare and may be congenital or acquired The acquired types are chiefly due to syphilis or bacterial endocarditis. The congenital aneurysms are usually attributed to developmental defect in either the aorticopulmonary septum or the elastic tissue of the aortic sinuses Diagnosis during the patient's lifetime with the aneurysm in an unruptured state can be made by angiocardiography (FIG 24) [21, 23]

Pulmonary veins In 1949, partial anomalous insertion of the right pulmonary vein into the inferior vena cava was first diagnosed during life by angiocardiography and cardiac catheterization Since then, recognition of totally anomalous pulmonary drainage into the right atrium and its tributaries has also become

Fig 25—(D) The pulmonary venous return from both lungs enters a common channel (*arrow*) which follows the course of a persistent left superior vena cava (PV) and this in turn empties into the left innominate vein



SVC

PA

RA

RV

Fig 26—Jet sign of anomalous pulmonary veins entering the junction of the superior vena cava ... pointing to defect at site of un- ...nd right atrium (RA). The right

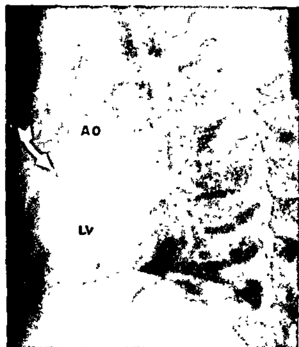


FIG 24—Marfan's syndrome in a 2 year old twin with aneurysmal dilatation of the aortic sinuses Arrow points to the aortic sinuses The left ventricle (LV) and aorta (AO) are opacified



FIG 25—Figure of eight deformity of the supracardiac structures due to anomalous pulmonary venous drainage into left innominate vein (A) Conventional frontal roentgenogram shows the classical "hilar and mediastinal shadows of anomalous pulmonary venous drainage into the left innominate vein



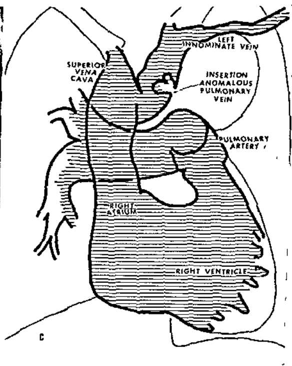


FIG 25—(B) The frontal angiocardiogram with defect in left innominate vein (arrow) (C) Tracing of B



FIG 28—Angiocardiogram showing the progression of contrast material from both subclavian veins into the superior vena cava and right heart as a bolus

small statures frequently permitted seeing the abdominal aorta when the left heart was opacified Later, when a technic for nephrography was developed, the abdominal aorta was occasionally seen, but this never occurred as frequently as during nephrotomography.

The intravenous method of abdominal aortography and peripheral arteriography depends on the principles developed for angiocardiography over 20 years ago and involves the making of rapid, simultaneous and bilateral injections into the arm veins Speed of injection of the contrast material is essential, and this is accomplished by the simultaneous injection into the large veins of both arms (FIG 27) This eliminates the factor of dilution of the contrast material by blood from the opposite innominate vein when only one injection is made and, of course, increases the bolus effect of the contrast material into the circulation (FIG 28) Speed of injection is also facilitated by elevating the arms and having the patient perform respiratory maneuvers

The time of roentgen exposure of the abdominal aortic or peripheral arteriogram is determined by the preliminary circulation time with sodium dehydrochlorate (Decholin). Standard roentgen technic similar to that for intravenous pyelography, which utilizes the Bucky grid and the making of a 2 second roentgen exposure of the film, is all that is needed for roentgenography of the abdominal aorta and its branches. No special radiographic equipment is required. A portable roentgen

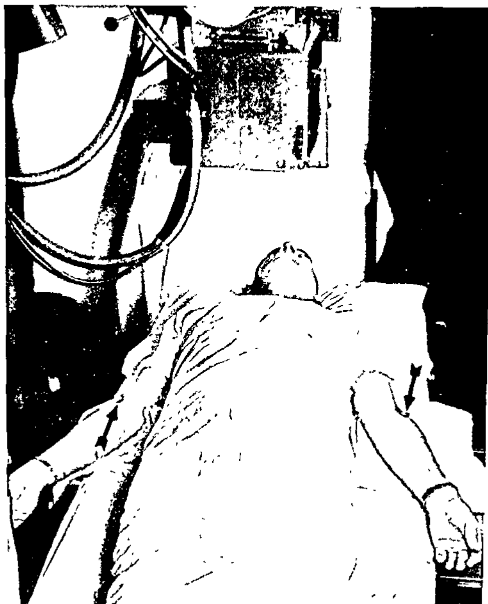


FIG 27 —Technic of intravenous abdominal aortography The patient is supine on a roentgen table which contains a Bucky grid cassette Robb-Steinberg needle stop-cock units (*arrow*) are then inserted into the large veins of both cubital spaces The patient is then ready for the simultaneous bilateral injection of concentrated contrast material in Robb-Steinberg special syringes

conventional chest roentgenogram suggested the diagnosis because of an anomalous pulmonary vessel at the right base Angiocardiography (FIG 26) confirmed the diagnosis by showing the newly recognized "jet sign," a filling defect at the site of insertion of the anomalous veins into the junction of the superior vena cava and right atrium, and the demonstration of the insertion of the anomalous veins The filling defect is due to the turbulence created by the anomalous pulmonary venous blood flow

Physiology of Intravenous Abdominal Aortography, Peripheral Arteriography and Cerebral Angiography

Opacification of the abdominal aorta was often secured during angiocardiography with the Robb-Steinberg method This was especially true in infants and children because their



FIG 30—Intravenous peripheral arteriography The normal femoral arteries

second injection was needed for more complete opacification Only 2 patients had studies of the cerebral circulation Among the noteworthy findings were arteriosclerotic abdominal aortic and splenic artery aneurysms, a ruptured spleen, a postlaminectomy aortico-inferior vena cava fistula, and arteriosclerotic (abdominal aortic and peripheral) endarteritis. The intravenous method of abdominal aortography, peripheral arteriography and cerebral angiography will very likely make arterial puncture for visualization of the cerebral, abdominal aortic and peripheral arterial system unnecessary. It already has made translumbar aortic puncture obsolete.

SUMMARY

Not all the physiologic data provided by roentgenography have been discussed in this chapter Rather, a practical approach to the way roentgen physiology enters into the every day practice of the internist who deals with the cardiovascular system has been emphasized. For instance, while poststenotic dilatation of the pulmonary artery and aorta have been illustrated, the physiologic concept regarding



FIG 29—The first intravenous abdominal aortogram with the method of bilateral, rapid and simultaneous injection of contrast material

apparatus, with exposure for two seconds at the completion of the abdominal study, is used for visualizing the peripheral vascular circulation.[28]

The first successful abdominal aortogram, made with the method of rapid, bilateral, simultaneous intravenous injection of concentrated contrast material and prediction of abdominal opacification was made on March 31, 1959 (FIG 29) The normal femoral arterial circulation is shown in FIGURE 30 To date, a total of 82 patients have had only mild and transient heat sensations after the equally divided intravenous injections of highly concentrated mixtures of contrast substances (average total dose, 1 cc/Kg.) The abdominal aorta and peripheral arteries were well visualized in all but one instance In 12 patients, a

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their formation has been omitted Instead, the reader is referred to the classic paper on this subject by Holman[9] Pulmonary edema has not been discussed and yet the observations of Robb in this condition provided the stimulus for development of the method of visualization of the cardiovascular system by concentrated contrast materials[18, 20]

A vast amount of cardiovascular physiology has been learned from rapid cineangiocardiography in animals[16, 17] Campeti has also described measurements to determine cardiac function in human cineangiocardiographic studies[2] Lind and Wegelius[12] utilizing multiple serial biplane angiocardiography have made fundamental studies of the fetal circulation These authors have also made graphic studies of the circulation[13]

Many correlative studies of angiocardiography and mitral valvular disease have also appeared[10, 15] Figley[6] and Stauffer et al[20] have recently discussed the role of angiocardiography in cardiovascular physiology while Dotter and Frische propose that blood flow be studied by injection of contrast particulate matter into the circulation[4]

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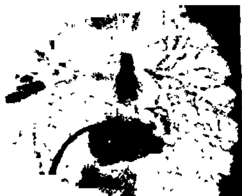






Fig 1—Severe valvular pulmonic stenosis (A) with secondary work hypertrophy of the right ventricular outflow tract below the obstructed valve (B) is demonstrated by selective opacification of the right ventricle with the patient in the left anterior oblique projection The subvalvular obstruction demonstrated in these photographs disappears in the diastolic phase of the heart cycle This does not indicate a true "fixed" type of infundibular obstruction It may be expected to disappear in from 10 to 14 months after effective correction of the valve obstruction has been accomplished

Fig 2—Segmental hypoplasia of the pulmonary arteries demonstrated by right ventricular opacification (P.A projection) There is marked narrowing of both pulmonary arteries (A) beyond the bifurcation of the main pulmonary artery trunk (B) The distal branches of both vessels beyond the hilar level are larger in diameter than the proximal vessels from which they are derived

Cinecardioangiography

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CINECARDIOANGIOGRAPHY is the technic of x-ray motion picture photography of the passage of radiopaque contrast media through the central circulation, following its rapid injection into one of the heart chambers or into a major vessel in immediate proximity to the heart It represents a combination of cardiac catheterization and angiocardiographic methods, which have been made possible by the development of the fluoroscopic image amplifier

An efficient image amplifier increases the brightness of a fluoroscopic image to levels which permit chest fluoroscopy to be performed in a well lighted room with less than 50 per cent of the x-ray dosage required for conventional fluoroscopic observation of similar subjects in total darkness The "amplified" image is bright enough to be photographed with an optical motion picture camera at a rate of 60 frames per second with less radiation than is required for adequate exposure of 6 to 8 full-sized radiographs per second by conventional angiocardiographic technics

Commercially available image amplifiers are equipped with a variety of optical viewing systems which permit the operator to observe the image being photographed The physical capacity of the system to provide fluoroscopy with a minimal x-ray dose and high-speed motion picture photography *during simultaneous fluoroscopic observation* has made it possible to combine easily cardiac catheterization and angiocardiographic technics in a single diagnostic procedure

Many of the limitations of conventional venous angiocardiography have been overcome by the development of methods for deliberately opacifying selected areas in either the right or left sides of the heart, to demonstrate specific anatomic defects This makes it possible to secure maximum contrast in the desired area of the heart with a minimum volume of contrast media. It reduces the problem of simultaneous opacification of overlapping structures, which often frustrates recognition of obvious defects.

With gradually increasing experience it has been found that radiopaque media may be safely injected into any area of the central circulation except into a normal coronary sinus, a "wedged" pulmonary artery or vein, or directly into an occluded coronary artery. Accidental injections into the coronary sinus have resulted in rupture of the sinus, leading to the development of cardiac tamponade and death Injections into occluded pulmonary arteries or veins have been made without recognizable injury but are capable of causing damage to the lung parenchyma Temporary occlusion of the orifice of a coronary artery with a catheter causes myocardial ischemia which may lead to the development of potentially fatal ventricular arrhythmias If flow through a coronary artery is obstructed by its occlusion with a catheter tip, a metabolic deficit will occur in the myocardium within 10 to 30 seconds It should be emphasized that, in the doses to be described, injections of contrast media into the root of the aorta or left heart chambers are no more hazardous than those made into any area of the right heart

To exploit fully the possibilities of selective intracardiac opacification it is usually necessary to perform multiple serial injections during the course of a single diagnostic study. Most authorities in the field of angiocardiography agree that more than two serial injections of contrast media are contraindicated [1, 2] This has been a major reason for the development of expensive and complex biplane angiocardiographic equipment By reducing the size of individual doses this limitation has been effec-

The studies have been supported in part by Research Grant No H-2795 from the National Institutes of Health

observed during continuing motion picture photography as it passes through the lungs to opacify the left atrium and ventricle. This will usually demonstrate the location of left-to-right shunts at the atrial, ventricular or aortic levels The density of contrast provided by such visualization is adequate to show isolated left-to-right shunts It fails to demonstrate multiple coexisting shunts and is often inadequate to define the exact location and size of communications between the atria or ventricles

The bifurcation of the pulmonary artery is selected for primary direct opacification to demonstrate the presence of large patent ducti or aortic pulmonary fistulae in patients with severe pulmonary hypertension. Although these lesions may cause only a left-to-right shunt under normal physiologic conditions, sudden overdistention of the pulmonary artery by the rapid injection of media will transiently reverse the shunt and cause momentary opacification of the aorta.

Selective filling of the right and left pulmonary arteries is used to demonstrate pulmonary arteriovenous fistulae of the lung, or partial and complete forms of anomalous pulmonary venous drainage to the right atrium or superior vena cava. Anomalous veins from the right lung may be more adequately demonstrated by catheterization of the veins involved from the right atrium or superior cava, with demonstration of their anatomic connections by injecting small quantities of media directly into their orifices (Fig 5)

In some patients, it is possible to catheterize the ascending aorta from the right ventricular outflow tract, but the pulmonary artery may not be successfully entered with the catheter tip In this situation, an injection of contrast media made immediately above the aortic valve annulus will reveal the presence of pulmonary artery trunks or bronchial communications arising from a truncus arteriosus, or rule out the possibility that any significant contribution to pulmonary flow is derived directly from the aorta (Fig. 4). Whenever this problem is encountered, a second injection should be made into the right ventricle, since this will frequently demonstrate a direct com-



Fig 4—Selective opacification of the ascending aorta, approached from the right ventricular outflow tract by way of a high interventricular septal defect, demonstrates the absence of any communication between the aorta and pulmonary arteries and the absence of any unusual bronchial collateral channels to the lungs. Note incidental opacification of the major trunks of the left coronary artery

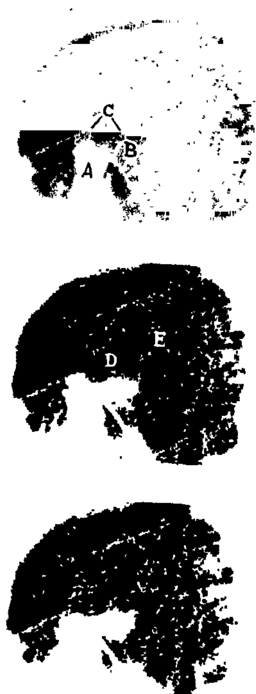


FIG 3 —A truncus arteriosus is demonstrated by injection of contrast media into the right ventricle (A) with the patient in the left anterior oblique position A large interventricular septal defect permits opacification of the left ventricle (B) The aortic valve annulus (C) over-rides the septal defect. A single aortic trunk (D) arises from the heart A large pulmonary artery (E) is derived from the aortic trunk and shows no direct communication with either ventricular chamber

tively overcome with presently available compounds.[3] From 3 to 6 serial injections of 90 per cent Hypaque have been made in more than 800 personally observed patients without any injury attributable to toxicity of the media Individual doses are limited to 0 3 cc per pound of body weight except in the presence of large left to right shunts, when they may safely be increased to a maximum of 0 5 cc per pound of body weight In patients without shunts weighing more than 100 pounds the dose is reduced to 0 25 cc per pound. It is desirable to allow a minimum of 10 and preferably 15 minutes to elapse between serial injections

Congenital Heart Disease

In the study of patients with suspected congenital lesions, right heart catheterization is performed, using an approach from the saphenous or superficial femoral veins The most advantageous potential locations for obtaining contrast visualization are determined after pressure measurements and blood oxygen determinations of all heart chambers and great vessels entered with the catheter tip In each instance there is an attempt to select areas for opacification which, after proper positioning of the patient, will most precisely define the anatomic nature of the defect and rule out all other differential possibilities, with the least number of serial injections

The right ventricle is selectively opacified to demonstrate obstructions in the right ventricular outflow tract, valvular pulmonic stenosis (FIG 1) or segmental hypoplasia of the pulmonary arteries (FIG 2) Selective right ventricular opacification will demonstrate an interventricular septal defect by direct passage of media across the septum into the left ventricle, if right ventricular pressure is more than 70 per cent as high as that in the left ventricle Injections into the right ventricle, made in the left anterior oblique projection, will demonstrate the relationship of the aortic valve annulus to the plane of the interventricular septum in patients with transposition of the great vessels, tetralogy of Fallot and truncus arteriosus (FIG 3).

Media injected into the right ventricle is

observed during continuing motion picture photography as it passes through the lungs to opacify the left atrium and ventricle. This will usually demonstrate the location of left-to-right shunts at the atrial, ventricular or aortic levels. The density of contrast provided by such visualization is adequate to show isolated left-to-right shunts. It fails to demonstrate multiple coexisting shunts and is often inadequate to define the exact location and size of communications between the atria or ventricles.

The bifurcation of the pulmonary artery is selected for primary direct opacification to demonstrate the presence of large patent ducti or aortic pulmonary fistulae in patients with severe pulmonary hypertension. Although these lesions may cause only a left-to-right shunt under normal physiologic conditions, sudden overdistention of the pulmonary artery by the rapid injection of media will transiently reverse the shunt and cause momentary opacification of the aorta.

Selective filling of the right and left pulmonary arteries is used to demonstrate pulmonary arteriovenous fistulae of the lung, or partial and complete forms of anomalous pulmonary venous drainage to the right atrium or superior vena cava. Anomalous veins from the right lung may be more adequately demonstrated by catheterization of the veins involved from the right atrium or superior cava, with demonstration of their anatomic connections by injecting small quantities of media directly into their orifices (FIG. 5).

In some patients, it is possible to catheterize the ascending aorta from the right ventricular outflow tract, but the pulmonary artery may not be successfully entered with the catheter tip. In this situation, an injection of contrast media made immediately above the aortic valve annulus will reveal the presence of pulmonary artery trunks or bronchial communications arising from a truncus arteriosus, or rule out the possibility that any significant contribution to pulmonary flow is derived directly from the aorta (FIG. 4). Whenever this problem is encountered, a second injection should be made into the right ventricle, since this will frequently demonstrate a direct com-



FIG. 4.—Selective opacification of the ascending aorta, approached from the right ventricular outflow tract by way of a high interventricular septal defect, demonstrates the absence of any communication between the aorta and pulmonary arteries and the absence of any unusual bronchial collateral channels to the lungs. Note incidental opacification of the major trunks of the left coronary artery.



Fig 3—A truncus arteriosus is demonstrated by injection of contrast media into the right ventricle (A) with the patient in the left anterior oblique position A large interventricular septal defect permits opacification of the left ventricle (B) The aortic valve annulus (C) over-rides the septal defect A single aortic trunk (D) arises from the heart A large pulmonary artery (E) is derived from the aortic trunk and shows no direct communication with either ventricular chamber.

tively overcome with presently available compounds.[3] From 3 to 6 serial injections of 90 per cent Hypaque have been made in more than 800 personally observed patients without any injury attributable to toxicity of the media Individual doses are limited to 0 3 cc per pound of body weight except in the presence of large left to right shunts, when they may safely be increased to a maximum of 0 5 cc per pound of body weight In patients without shunts weighing more than 100 pounds the dose is reduced to 0 25 cc per pound. It is desirable to allow a minimum of 10 and preferably 15 minutes to elapse between serial injections

Congenital Heart Disease

In the study of patients with suspected congenital lesions, right heart catheterization is performed, using an approach from the saphenous or superficial femoral veins The most advantageous potential locations for obtaining contrast visualization are determined after pressure measurements and blood oxygen determinations of all heart chambers and great vessels entered with the catheter tip In each instance there is an attempt to select areas for opacification which, after proper positioning of the patient, will most precisely define the anatomic nature of the defect and rule out all other differential possibilities, with the least number of serial injections.

The right ventricle is selectively opacified to demonstrate obstructions in the right ventricular outflow tract, valvular pulmonic stenosis (Fig 1) or segmental hypoplasia of the pulmonary arteries (Fig 2). Selective right ventricular opacification will demonstrate an interventricular septal defect by direct passage of media across the septum into the left ventricle, if right ventricular pressure is more than 70 per cent as high as that in the left ventricle Injections into the right ventricle, made in the left anterior oblique projection, will demonstrate the relationship of the aortic valve annulus to the plane of the interventricular septum in patients with transposition of the great vessels, tetralogy of Fallot and truncus arteriosus (Fig 3)

Media injected into the right ventricle is

aorta, resulting in satisfactory demonstration of ventricular septal defects, mitral or aortic stenosis, coarctation of the aorta and communications between the aorta and pulmonary artery. When the communication between the atria is a true interatrial septal defect or an unusually large foramen ovale with an incompetent valve, left atrial injections provide ideal demonstration of the lesion by direct passage of media across the defect into the right atrium Under these circumstances the right atrium, ventricle and pulmonary artery may be so heavily opacified that a coexisting ventricular septal defect or patent ductus arteriosus may not be recognized, and direct left ventricular opacification is indicated

The left ventricle can usually be catheterized from the left atrium across the mitral valve Occasionally, this proves to be technically impossible, and retrograde aortic catheterization is used to enter the left ventricle across the aortic valve by an approach from the superficial femoral or right brachial arteries (Fig 6)

Left ventricular opacification will precisely demonstrate the presence, location and size of interventricular septal defects Mechanically significant obstructions in the left ventricular outflow tract or at the aortic valve annulus are easily recognized. In mitral regurgitation selective opacification of the left ventricular chamber demonstrates reflux of contrast media across the valve into the left atrium[4] If this does not occur, mitral insufficiency may be excluded as a diagnostic possibility. Occasionally, small quantities of media may be seen crossing the valve in cases with no true mitral insufficiency, because of the occurrence of ectopic ventricular contractions during the period of injection, or in cases of posterior displacement of the valve cusp by the catheter. This artifactual type of regurgitation may lead to a false positive diagnosis, but is usually recognizable by its inconsistency during serial ventricular contractions, and the relatively small quantity of media seen entering the left atrial chamber

The technics described for the demonstration of specific intracardiac lesions commonly encountered in patients with congenital heart disease are based on the usual physiologic conditions associated with specific anomalies

Valvular Heart Disease

Following a statistically significant experience in the study of patients with congenital malformations and aided by the development of image amplifiers providing a larger field size than that originally available, selective methods of contrast visualization are now being used in the study of patients with acquired valvular and coronary artery disease. If the various aspects are fully considered in planning each individual diagnostic procedure, dependable visualization of any potential combination of defects may be reasonably anticipated.

In patients who present clinical evidence of combined mitral stenosis and insufficiency, or an aortic valve lesion, retrograde aortic catheterization is performed from the right brachial artery in the antecubital fossa A dilute solution of heparin is injected into the artery below the point of temporary occlusion to minimize the possibility of distal thrombosis during the period of occlusion. The catheter is passed down the ascending aorta to a point immediately above the aortic valve ring After aortic pressure has been measured, the catheter is passed retrograde across the valve into the left ventricle This is accomplished without force during ventricular systole by manipulating the catheter tip back and forth across the valve orifice at a point slightly above that where resistance to downward progress to the catheter tip is encountered in the ascending aorta Of 430 patients in whom this has been attempted, failure to cross the valve has occurred in only 13 instances Contrary to expectations, the presence of aortic stenosis does not preclude the possibility of retrograde left ventricular catheterization from the aorta One hundred and twelve of these patients have shown clinical evidence of the presence of aortic stenosis, the most severe of which demonstrated a systolic pressure gradient of 180 mm Hg across the valve ring Ten of the 13 failures to cross the valve occurred in this group The other 3 occurred in patients with no evidence of an aortic valve lesion

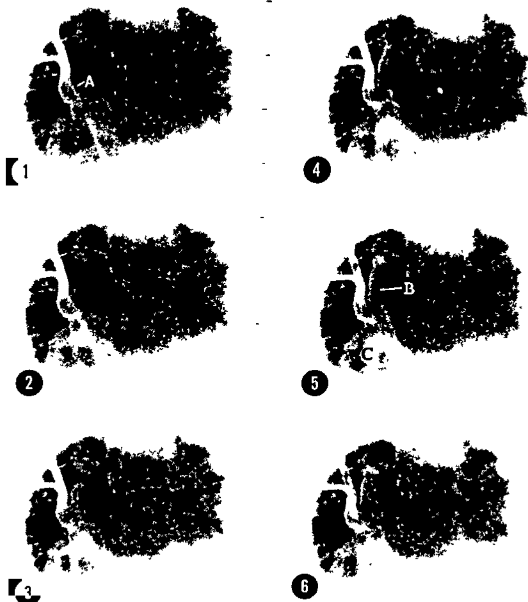


FIG 5—An anomalous right superior pulmonary vein draining into the right atrium near the orifice of the superior vena cava is demonstrated by slow injection of contrast media into the orifice of the pulmonary vein (A) in frames 1, 2 and 3 During the injection, the catheter is withdrawn into the heart (frames 4, 5 and 6) Demonstrating the relationship of the superior vena cava (B) and right atrium (C) to the orifice of the anomalous vein

munication to the pulmonary circulation from the right ventricle, even though catheterization of the pulmonary artery may not be accomplished On the other hand, such an injection may confirm the fact that all blood flow to the lungs is derived from the aorta (FIG 3)

Selective opacification of the left atrium, left ventricle or both is performed whenever a communication at the atrial level permits catheterization of the left atrium by way of an atrial septal defect or a patent foramen ovale If the interatrial communication is a patent foramen ovale with a competent valve, media introduced into the left atrium does not cross the communication to opacify the right atrium but follows a normal course through the mitral valve orifice to the left ventricle This permits excellent opacification of the left ventricle and

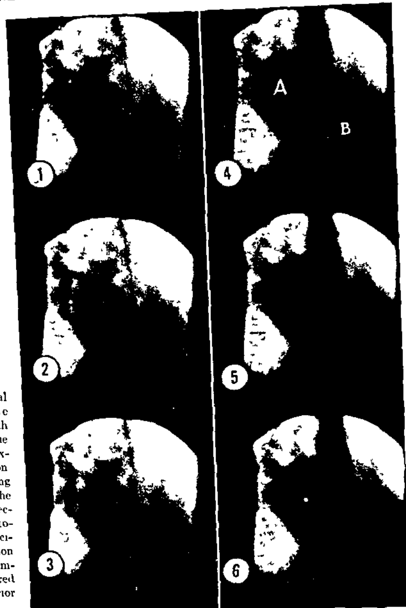


FIG 7—A moderate degree of mitral regurgitation is demonstrated by selective opacification of the left ventricle with the patient in the right anterior oblique projection Frames 1, 2 and 3 were exposed immediately prior to the injection Frames 4, 5 and 6 were exposed during the second systolic contraction after the injection was made. It is possible to recognize in reproduction of still photographs that the left atrium (A) is opacified from the left ventricle (B) Motion picture projection, however, easily demonstrated that the regurgitation occurred across a localized defect in the posterior aspect of the valve annulus

cardia or ventricular fibrillation may occur, although this has never personally been observed

In patients with rheumatic heart disease, contrast media injected directly into the left ventricle during motion picture photography provides excellent demonstration of the severity and often the anatomic characteristics of an incompetent mitral valve If media fails to cross the valve with an adequate injection, mitral regurgitation may be excluded as a diagnostic possibility (FIG 6). In some patients, severe dilatation of the valve ring is demonstrated by a tremendous regurgitant surge of media retrograde across the annulus, followed by extremely slow clearing of the left atrium and ventricle. In others, only a small jet of media is seen to cross the central or posterior aspect of the annulus (FIG 7). Usually, three to five systolic contractions are required to clear the ventricle of media Occasionally, one or two premature contractions occur during the injection, which may result in artifactual, inconstant and usually slight regurgitation of media into the left atrium This is easily recognized by observation during the period of injection If concern over possible misinterpretation exists, the catheter should be slightly re-

Left ventricular pressure is measured as soon as the catheter tip passes into the left ventricular chamber If systolic pressure is less than 20 per cent higher than that measured in the ascending aorta, it is doubtful that enough mechanical obstruction to blood flow exists to justify an attempt at aortic valvulotomy, even though obvious clinical signs of aortic stenosis are present The catheter tip is passed down to the apex of the left ventricle to a point where slight resistance is felt It is then withdrawn to a position midway between the cardiac apex and the level of the aortic valve Premature ventricular contractions occur if the catheter beats forcibly against the ventricular wall in the vicinity of the cardiac apex These are abolished as the tip is withdrawn to the central area of the ventricular chamber. If excessive endocardial stimulation by the catheter tip is allowed to persist, ventricular tachy-

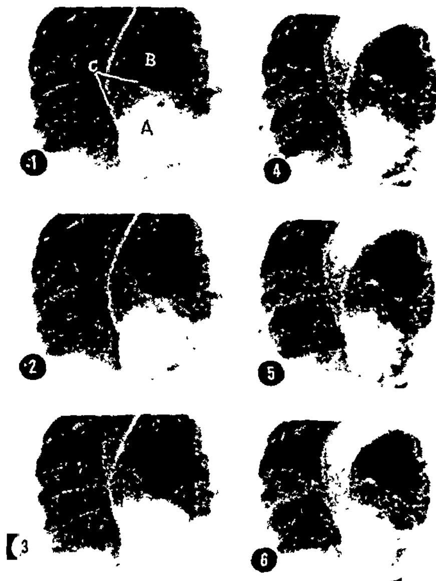


Fig 6—Selective opacification of the left ventricular chamber (A) catheterized from the ascending aorta rules out the possibility of mitral regurgitation when no media crosses the valve annulus into the left atrium (B) Frames 1, 2 and 3 were exposed during early systole The media crosses the plane of the aortic valve (C) without evidence of obstruction Frames 4, 5 and 6 were exposed during the late phase of the following systole The patient was placed in the left anterior oblique position



FIG 8—Aortic stenosis demonstrated by selective opacification of the left ventricle, (A) catheterized from the ascending aorta, with the patient in the left anterior oblique position The plane of the aortic valve annulus (B) in early systole is shown in frame 2 In early systole, an asymmetric jet of media (C) crosses the left anterior leaflet of the valve to fill the ascending aorta (D) The right anterior and noncoronary leaflets are fused and fail to open normally

concentrated media were injected under pressures of 10 Kg/cm.² In several instances, very heavy opacification of one vessel was obtained, with no visible evidence of filling in its counterpart This accidental "selective" opacification of one coronary artery was not accompanied by the development of arrhythmias, which had been feared as a potential consequence of producing transient inequality in the distribution of oxygen and metabolites to the myocardium

In October of 1958, deliberate attempts to perform "selective" coronary arteriograms were initiated Serial injections of 20 to 30 cc. of contrast media were made slowly, over a period of three to six seconds, directly into the right and left anterior sinuses of Valsalva, using the 5 inch image amplifier with a 35 mm. camera for photographic recording of the passage of media through the individual vessels. This resulted in adequate visualization of both

positioned in the ventricular chamber and a second injection made into the ventricle before it is withdrawn

The functional and anatomic characteristics of aortic valve lesions are evaluated by pressure measurements and selective injections of contrast media into the left ventricle and into the ascending aorta In patients with clear-cut clinical evidence of aortic stenosis, systolic pressure gradients across the valve have ranged from 0 to as high as 180 mm Hg. Some of the former patients have demonstrated heavy valve calcification with thickening and immobility of a valve cusp but a freely mobile and wide open area involving at least half the diameter of the valve ring By anatomic definition, these patients undoubtedly have aortic stenosis but with no serious mechanical burden imposed on the left ventricle In certain patients, severe coexisting coronary artery disease may be the real cause of the syncopal attacks or angina pectoris This conclusion may be positively supported by simultaneously performed cine-coronary-arteriograms

In patients with severe aortic stenosis, photographic demonstration of the valve obstruction has been somewhat disappointing as compared to the demonstration of severe obstruction at the pulmonary valve The valve itself is seen as a thickened, relatively immobile dome, above the level of the valve annulus The jet of media characteristically observed in the dilated pulmonary artery above a stenotic pulmonary valve is not seen, possibly because the stream of media across the valve is modified by the catheter extending down from the aorta through the valve orifice (Fig. 8)

Aortic regurgitation is demonstrated by injection of media into the ascending aorta with the catheter tip placed about 1 inch above the valve annulus. To avoid artifactual production of aortic regurgitation it is important that the catheter tip be placed above the maximum upward deflection of the valve cusps, and that the use of an end-hole catheter be avoided Such a catheter may direct a jet of media retrograde across the valve, against the stream of ventricular ejection, during the systolic phase of the heart cycle. Minor and severe degrees of aortic regurgitation (Fig 9) are clearly recognized by this technic, and the differential diagnosis between aortic and pulmonic insufficiency in the presence of a mitral valve lesion is easily resolved

Coronary Artery Disease

Cine-coronary-arteriography is at the present time in an embryonic stage of development as a diagnostic method In several hundred patients with congenital and acquired valvular heart disease, heavy opacification of coronary arteries was recognized as an incidental consequence of selective opacification of the left heart chambers or the root of the aorta This did not produce symptoms or objective electrocardiographic evidence of myocardial injury or hypoxia.

In 1956, a series of experiments was conducted with the aid of W J Kolff and Edward Miller on dogs, using a 5 inch image amplifier, to study the possible feasibility of coronary arteriography These demonstrated that, by flooding the aortic root with contrast media in doses of 0 3 to 0 5 cc /lb , under a pressure of 10 Kg /cm², the coronary arteries could usually be opacified It was possible to demonstrate sites of partial constriction or total occlusion in major arterial trunks caused by previous surgical ligation Areas of inflammation in the epicardium due to previous implantation of nonradio-opaque foreign bodies were easily demonstrated, and the success or failure of a number of attempts to perform arterial anastomoses or graft procedures was defined in the living animal At that time, it was believed that application of these technics to human problems must await the development of larger image amplifiers

In 1958, an 11 inch image amplifier equipped with a Schmidt optical system and a 35 mm camera was made available for this purpose. Incidental coronary arteriograms were performed by flooding the aortic root in a series of 50 patients with rheumatic valve lesions, in whom there was no clinical evidence of coronary artery disease These studies demonstrated that adequate opacification of both coronary arteries could be anticipated in fewer than 70 per cent of patients with normal vessels even though doses of from 40 to 60 cc. of

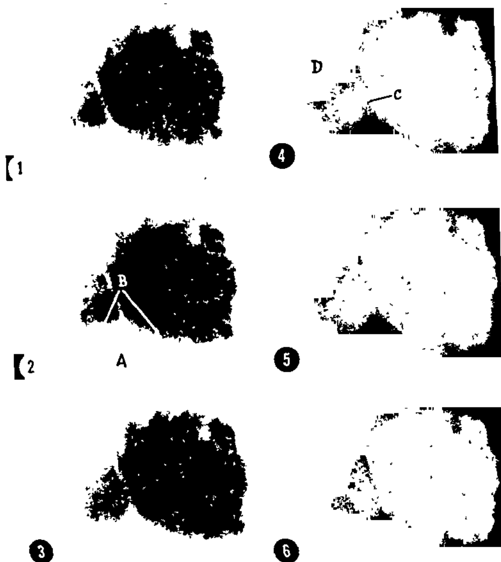


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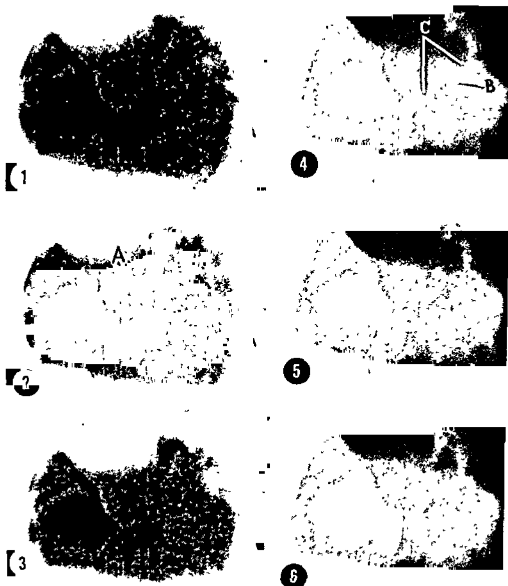


Fig 9—Aortic regurgitation demonstrated by selective opacification of the ascending aorta (A) in the left anterior oblique projection In early diastole (frame 3) a jet of media crosses the thickened valve annulus (C) to fill the left ventricle (B) The regurgitant stream persists through the diastolic phase of the heart cycle (frames 4, 5 and 6)

coronary arteries in more than 90 per cent of the 137 patients studied (Fig 10) Photographic reproduction of the five inch field on 35 mm motion picture frames provided better definition of the small structures under study than could be obtained when larger areas were reproduced on the same area of film emulsion The 5 inch image amplifier is large enough to cover the area of distribution of either coronary artery in the majority of patients, requiring only slight movement of the amplifier during the period of opacification

In April, 1959, a special catheter was made by the United States Catheter and Instrument Company, Glens Falls, New York, which was designed to permit direct catheterization of the human coronary orifices The external diameter of this woven radio-opaque catheter is 2 7 mm (8 F) Five cm from the tip, it tapers sharply to an external diameter of 1 6 mm (5 F) It has an open tip in addition to two pairs of opposed side openings in the distal 0 5 cm of its length The heavy body of the catheter provides enough rigidity for it to be ma-

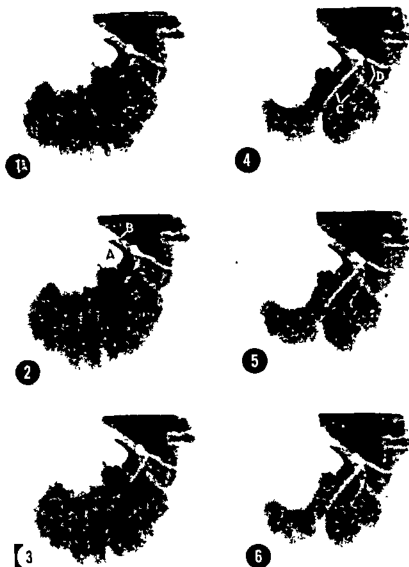


FIG 10—A normal left coronary artery is demonstrated by selective opacification of the left anterior sinus of Valsalva (A) with the patient rotated 30 degrees into the left anterior oblique projection Frames 1, 2 and 3 were exposed early in the period of injection and show the main trunk (B) and the bifurcation of the vessel Frames 4, 5 and 6 show more complete filling of branches of the anterior descending (C) and circumflex (D) branches Note the absence of aortic regurgitation

nipulated deliberately in the systolic jet immediately above the aortic valve Its small distal segment may be safely passed into the orifices of adult coronary arteries which usually exceed 3 0 mm in diameter This catheter has been used for selective opacification of both coronary arteries in more than 200 patients, representing all phases of the natural history of coronary artery disease The slow manual injection of from 3 cc to a maximum of 6 cc of contrast media by this technic provides uniformly dependable visualization of either vessel (FIG 11) In patients weighing less than 150 pounds, 75 per cent Hypaque or 76 per cent Renografin provides adequate contrast In larger patients, 90 per cent Hypaque or 85 per cent Cardiografin have been routinely used

As many as six serial injections of contrast

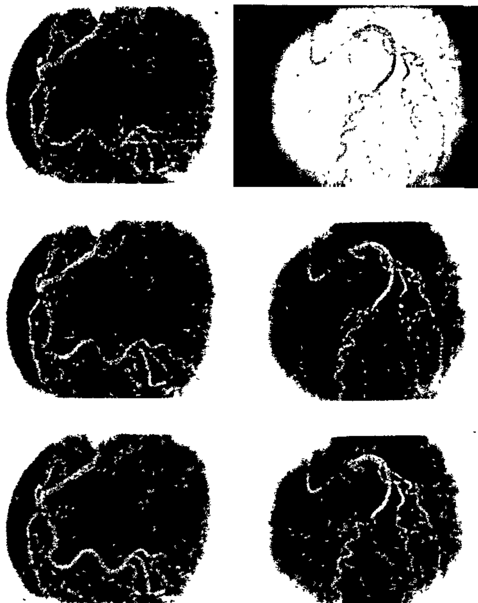


FIG 11—(A) A normal right coronary demonstrated by catheterization of its orifice and injection of 3 cc of contrast media directly into the vessel Patient rotated 60 degrees into L A O projection (B) The left coronary artery of the same patient, a 58 year old white male, demonstrated by injection of 3 cc of media into its orifice

media have been made into each coronary artery orifice at one to three minute intervals, using the media and doses described above, without evidence of myocardial injury In no instance has perfusion with the media resulted in the development of anginal pain, electrocardiographic evidence of myocardial ischemia, or photographic evidence of coronary artery constriction Serial injections into the same vessel usually show evidence of slight to moderate arterial dilatation This, however, is considerably less marked than the vasodilatation seen in the same subjects following administration of nitroglycerin, sublingually With very heavy coronary opacification, transient depression or elevation of the T wave in the electrocardiogram occurs at the moment when the media is in maximum concentration in the arteriolar and capillary bed of the perfused myocardium This is accompanied by bradycardia. A gradual return of T waves and heart rate to the preinjection state occurs during the follow-

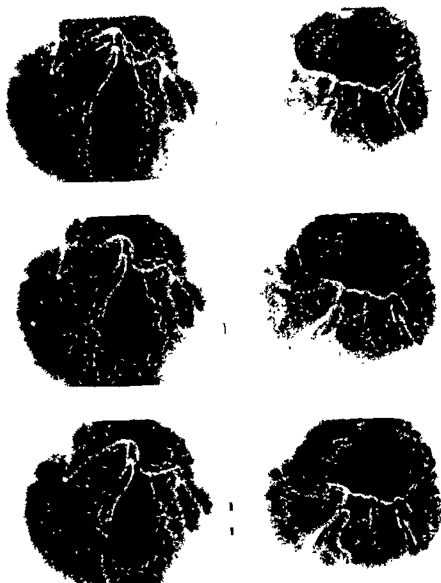


FIG 12—(A) Marked segmental narrowing of the proximal segment of the left anterior descending coronary artery (*arrow*) immediately beyond its origin from the left main coronary artery trunk demonstrated by injecting 4 cc of media into the left main coronary artery Exposures were made with the patient rotated 45 degrees into L A O position (B) Complete occlusion of a short segment of the circumflex coronary artery (*between arrows*) demonstrated by injection of 4 cc of media into left main coronary artery A small vessel arising from the circumflex artery above the occluded segment "bridges the gap" and permits opacification of the artery beyond the point of segmental obstruction Note anterior descending trunk also shows segmental narrowing above its primary bifurcation

ing 10 to 20 seconds This may be accelerated by asking the patient to take one or two deep full breaths

It is impossible to overemphasize the obvious fact that the fundamental hazard involved in the application of this technic lies in the possibility of inadvertent mechanical occlusion of a coronary artery with the catheter tip If the tapered catheter described above is employed, this possibility is statistically remote If such occlusion occurs, constantly monitored pressure records from the tip become mechanically damped, and are instantly recognizable on a monitoring oscilloscope *This demands immediate withdrawal of the catheter tip back into the ascending aorta* If the

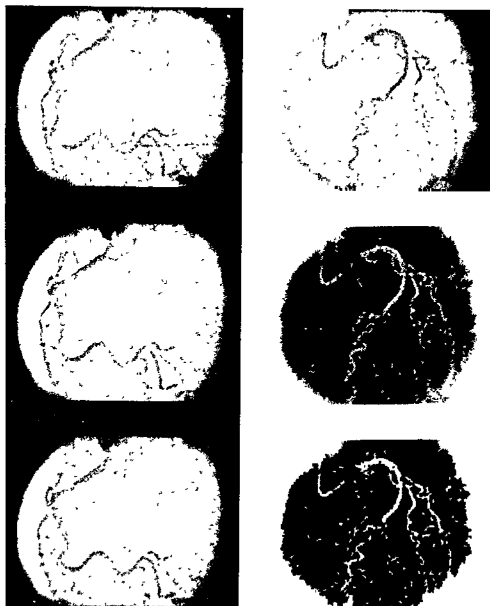


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Methods for the Study of the Circulation in Man

Cardiac Catheterization, Indicator-Dilution Curves and Related Technics

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Right Heart Catheterization

THE ability to record pressure pulses from the cardiac chambers and great vessels in man has permitted the hemodynamic analysis of a variety of physiologic and pathologic states. More than any other single influence, the development of cardiac catheterization has been responsible for the rapid advances in clinical cardiovascular physiology during the past two decades.

The technic of right heart catheterization consists of the introduction of a plastic, radiopaque catheter into the venous system. In adults, the catheter is generally introduced into the left antecubital vein with the aid of local anesthesia. In infants and young children, right heart catheterization is generally carried out under heavy sedation or general anesthesia. The saphenous vein, or occasionally the femoral vein, is employed when the small size of the child's antecubital vein prohibits introduction of the catheter. Use of the saphenous vein facilitates the crossing of an atrial septal defect or a patent foramen ovale. Under fluoroscopic control, the catheter is passed through, pressures are recorded from and blood samples obtained from the venae cavae, the right atrium, right ventricle and pulmonary artery. With the tip of the catheter in the pulmonary artery, the cardiac output may be measured by the Fick method. Pressures and cardiac output may be determined in the resting state and during mild exertion, such as pedaling a stationary bicycle while in the recumbent position, or during strenuous exercise while in the erect position on a treadmill. The effect of drugs on pressure and output may also be investigated. Probing of the cardiac chambers and great vessels may reveal the presence of a congenital anatomic anomaly such as a communication between the two sides of the heart. Finally, the cardiac catheter may also be used for the selective injection either of indicator or of radiopaque dyes into the cardiac chambers.

The sampling of blood from the venae cavae, the chambers of the right heart and pulmonary artery, and the demonstration of an oxygen step-up as the catheter is advanced from one chamber to the next, has been the standard method for the detection, localization and quantification of left-to-right cardiac shunts. When the average right atrial oxygen content exceeds the average vena caval content by more than 1.5 volumes per cent, a left-to-right shunt at the atrial level is usually present. A step-up of 1.0 volumes per cent from right atrium to right ventricle or from right ventricle to pulmonary artery is generally sufficient evidence for the diagnosis of shunts into these areas. The value of the oxygen method for the detection of left-to-right shunts is limited by the changes in the patient's metabolic state during the time required for positioning the catheter and obtaining blood samples, as well as by incomplete mixing of blood in the venae cavae and right atrium. A recently introduced method avoids these limitations of the oxygen method. An inert foreign gas, such as Nitrous Oxide (N_2O) or Krypton[85] (Kr^{85}), is inhaled by the patient for 30 seconds. During this time the arterial level of the gas rises abruptly, but because of the solubility of the gas in the tissues, the level in the right side of the heart rises very slowly. In the presence of a left-to-right shunt the level

catheter is not promptly withdrawn, S-T segment displacement appears from 10 to 30 seconds later, coincident with the development of a metabolic deficit in the myocardium If this is allowed to occur, the patient will develop anginal pain or a ventricular arrhythmia For this reason, it is essential that pressure pulses from the catheter tip be monitored constantly during all phases of the procedure, except during the three to six seconds required to perform individual injections of contrast media

Selective opacification of individual coronary arteries by this method makes it possible to provide the following information:

1 The exact location of partial and complete occlusive lesions in major vessels as small as 1 mm in diameter may be demonstrated (Fig 12A).

2 The length of the obstructions may be defined (Fig 12B)

3 The origin and distribution of collateral arterial channels as small as 100 micra in lumen diameter are clearly demonstrated This has made it possible to define the presence, anatomic characteristics, and functional efficiency of intercoronary collateral channels in the living human with coronary artery disease

A greater experience with cine-coronary-arteriography must be attained before its potential range of usefulness and its limitations are defined It will be accepted as a clinically useful diagnostic tool, only if it can be safely employed to give completely dependable objective proof of the presence or absence of mechanically significant occlusive lesions The evidence so far available is assurance that this will be accomplished

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valve into the ascending aorta The bronchoscope and needle may then be removed and hemodynamic measurements carried out without the stress of bronchoscopy The chief advantage of this method appears to be its distinct safety when compared to other methods, while the major disadvantages are that the services of a skilled endoscopist are required and that the patient is subjected to the stress and discomfort of bronchoscopy.

The posterior transthoracic technic consists of the introduction of a needle into the left atrium, generally under fluoroscopic guidance, through a right paravertebral approach A plastic catheter passed through this needle then permits measurement of left ventricular and aortic pressures. The chief advantage of this method is the ease with which the left atrium may usually be punctured However, the development of pneumothorax, hemothorax and cardiac tamponade have been occasional complications In many large series of patients studied by this technic there have been one or more fatalities, usually due to cardiac tamponade Unexplained hypotensive episodes and the knotting of catheters within the heart requiring cardiotomy for extraction have also been observed following transthoracic left heart catheterization

A more recently introduced method, particularly suited for the study of children and of patients with aortic valvular disease, consists of percutaneous puncture of the left ventricle through the anterior chest wall This method, however, does not permit the measurement of left atrial pressure Another method of left ventricular catheterization consists of the passage of a standard cardiac catheter retrograde through a peripheral artery and across the aortic valve into the left ventricle. The left atrium, aortic arch and pulmonary artery may also be punctured directly through the suprasternal notch.

Transseptal left heart catheterization obviates many of the disadvantages inherent in the other methods and is now the technic of choice in our laboratory. Following the insertion of a special, thin-walled no 8F catheter into the right saphenous vein, its tip is advanced into the right atrium A curved, specially constructed, no 17 gauge needle is inserted into the catheter and is passed upward until its point lies just within the catheter tip in the right atrium With the metal arrow attached to the needle hub used as an indicator, the needle and catheter are rotated posteriorly and medially against the interatrial septum in the region of the fossa ovale. Under fluoroscopic guidance the catheter with the needle point still retracted is advanced toward the septum until resistance is encountered. The needle is then extended 1 5 cm. beyond the catheter tip. A sudden decrease in resistance is usually felt as the septum is punctured (Fig. 1). Left atrial pressure is then recorded from the needle. The lumen of the needle permits the passage of a polyethylene catheter for the measurement of left ventricular and aortic pressures. Puncture of the left atrium through the interatrial septum avoids external cardiac puncture and thereby obviates the hazard of pneumothorax or intrapericardial hemorrhage. This factor is probably responsible for the safety of the technic The venous

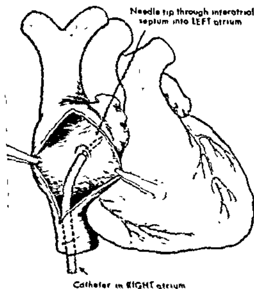


Fig 1—Diagrammatic representation of the position of the cardiac catheter and needle following puncture of the atrial septum (Reproduced by permission from Ross, J, Jr, Braunwald, E, and Morrow, A G Transseptal left atrial puncture. New technique for the measurement of left atrial pressure in man Am J. Cardiol *3*. 653, 1959)

of the foreign gas in the right heart distal to the shunt rises abnormally, and this permits recognition and quantification of even small left-to-right shunts.

When the tip of the catheter is wedged in a peripheral pulmonary artery, free communication is established between the lumen of the catheter and the pulmonary capillary venous bed. In the absence of an obstructing lesion between the pulmonary capillary bed and the left atrium, this makes possible an estimation of left atrial pressure There has been considerable controversy regarding the interpretation of pulmonary artery wedge pressures Part of this stems from improper technic which results in the introduction of numerous artifacts However, when fully saturated blood can be withdrawn from the catheter and when the pressure contour resembles that of an atrial pressure pulse, the mean pulmonary artery wedge pressure may be taken as a fairly accurate representation of the mean left atrial pressure In some instances, particularly in the presence of considerable left atrial hypertension, the contour of the left atrial pressure pulse is faithfully transmitted to the pulmonary artery wedge position However, in many patients the contour of the "wedge" pressure is considerably distorted when compared to the left atrial pressure pulse contour The analysis of the "wedge" pressure pulse has been of relatively little value in detecting the presence of significant mitral regurgitation in the preoperative study of patients with mitral valve disease

The recording of the *mean* pulmonary artery wedge pressure, however, adds considerably to the information derived from right heart catheterization In the absence of mitral valve dissease, the mean wedge pressure is a reasonably reliable index of mean left atrial as well as of left ventricular end diastolic (filling) pressure In patients with mitral stenosis, the pulmonary artery wedge pressure indicates the level of left atrial pressure When taken together with the cardiac output, it makes possible a rough estimation of the effective orifice size of the mitral valve The pulmonary vascular resistance can also be calculated when pulmonary artery and pulmonary artery wedge pressures as well as cardiac output are known.

Right heart catheterization may generally be considered to be a safe procedure; the mortality has been estimated at approximately 0.1 per cent It is obvious that the incidence of complications depends primarily on the type of patient studied and is highest in infants and children with cyanotic congenital heart disease. The chief danger of the procedure is the development of arrhythmias which result from contact of the catheter with the endocardium Several premature ventricular contractions are regularly observed as the catheter crosses the tricuspid orifice However, serious arrythmias such as supraventricular or ventricular tachycardia and even fatal ventricular fibrillation have occurred Constant monitoring of the electrocardiogram and the prompt discontinuation of the procedure in the face of persistent arrhythmias are essential to the safety of right heart catheterization. Rare hazards of right heart catheterization include knotting of the catheter within the heart, the development of bacterial endocarditis after the introduction of a contaminated catheter, thrombophlebitis, perforation of the heart by the catheter and vascular collapse in infants with serious heart disease following anesthesia, and repeated blood sampling

Left Heart Catheterization

The development of surgical procedures for the mitral and aortic valves focused attention on the necessity of recording pressure pulses from the left side of the heart Of the several methods available for left heart catheterization, the two which are most widely employed at the present time are the transbronchial and the posterior transthoracic technics The former method consists of the introduction of a bronchoscope to the level of the carina under suitable sedation and local anesthesia. A needle is then introduced through the bronchoscope, the left main stem bronchus is pierced and the needle is advanced through the wall of the left atrium which lies in close relation to the left main bronchus. Following measurement of left atrial pressure, a thin plastic catheter is advanced through the needle into the left atrium, across the mitral valve into the left ventricle and occasionally across the aortic

third rise of atrial pressure which has been termed the V wave. Its peak occurs at the end of isometric relaxation of the ventricles, at the instant of reopening of the atrioventricular valves. The resulting emptying of the atria is responsible for the y descent of the atrial pressure tracing. During the early or rapid phase of ventricular filling, the atrial and ventricular pressures decline rapidly. However, when blood continues to enter the well filled ventricle in mid-diastole, the ventricular pressure rises slightly. This rise in pressure is transmitted to the atria and results in a fourth elevation of atrial pressure during diastasis, the phase of slow ventricular filling.

There are only minor differences in the pressure pulses in the two atria. In the normal left atrial pressure tracing, the highest point during the cardiac cycle is recorded at the time of the peak of the V wave in aproximately one-half of all subjects, and at the peak of the A wave in the remainder. In contrast, the V wave is less prominent in the right atrium, in which the A wave generally produces the highest pressure during the cardiac cycle. Mean left atrial pressure normally exceeds mean right atrial pressure (TABLE I).

The normal atrial pressure pulse contour has been presented in considerable detail since its modification may be of considerable physiologic and diagnostic significance. In atrial fibrillation the A wave is absent, while in nodal rhythm it is generally superimposed on the C wave and x descent. In the presence of atrioventricular block, the atria contract against closed atrioventricular valves and giant A waves result.

Normal closure of the atrioventricular valves is dependent on the normal temporal sequence of atrial and ventricular contraction. When this sequence is disturbed, as in atrial fibrillation, atrioventricular dissociation, nodal or ventricular rhythms, a small degree of ventriculo-atrial reflux occurs early in ventricular systole before the atrioventricular valves close. This results in a prominent and prolonged C wave and abbreviation or even obliteration of the x descent. Such arrhythmias often produce fusion of the C and V waves and a plateau-shaped atrial pressure pulse.

In the presence of ventriculo-atrial regurgitation, during ventricular systole blood enters the atrium not only from its tributary veins but also from the ventricle, and results in a prominent v wave (FIG. 3). With severe de-

TABLE 1.—*Normal Hemodynamic Values*
(Pressures in mm Hg)

Site	Range
Right atrium (mean)	−2–+5
Left atrium (mean)	4–12
Right ventricle (systole)	16–30
Right ventricle (end diastolic)	0–7
Left ventricle (end diastolic)	4–12
Pulmonary artery (systolic)	12–30
Pulmonary artery (diastolic)	4–13
Pulmonary artery (mean)	8–19
Pulmonary artery wedge (mean)	5–13

Cardiac output 2.60 to 3.60 L./min./M² B.S.A.
Pulmonary arteriolar resistance less than 250 dynes/sec./cm⁻⁵

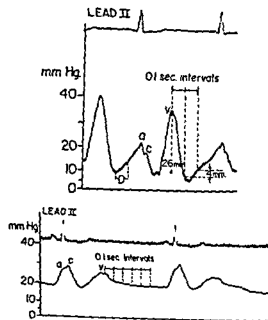


FIG. 3.—Left atrial pressure pulse from a patient with pure mitral regurgitation (*above*) and a patient with predominant mitral stenosis (*below*). In mitral regurgitation, the V wave is more prominent, and the y descent in the first 0.1 second of diastole is more rapid than in mitral stenosis. D refers to diastasis, present in mitral regurgitation, but absent in stenosis. (Reproduced with permission from MORROW, A. G., BRAUNWALD, E., HALLER, J. A., AND SHARP, E. H. The left atrial pressure pulse in mitral valve disease. A correlation of pressures obtained by transbronchial puncture with the valvular lesion. Circulation *16*: 399, 1957.)

approach permits both right and left heart catheterization to be conveniently performed in the course of a single study. In addition, the procedure causes no appreciable discomfort, and therefore prolonged measurements of pressures in the left side of the heart can be obtained. Transseptal left heart catheterization is also convenient to carry out in infants and children. Selective angiocardiograms with injections of contrast substance into the left atrium have also been performed through the transseptal needle. Finally, the method is technically simple and can be performed by any person trained in the usual technics of right heart catheterization.

One of the most important applications of the technics of catheterization of both sides of the heart has been the estimation of the severity of valvular stenosis. It is now quite clear that in the absence of anatomic obstruction the pressure gradient required to drive a normal cardiac output across cardiac valves is so small that it cannot be detected with present technics. However, as progressive valvular narrowing occurs, increased pressure is required upstream

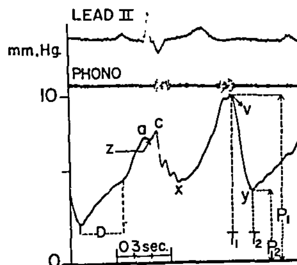


Fig. 2.—Normal left atrial pressure pulse obtained at transbronchial left heart catheterization. P_1 refers to the pressure at the peak of the V wave, while P_2 indicates the pressure at the nadir of the y drop. T_2–T_1 refers to the time interval required for this pressure drop. D refers to the period of diastasis. (Reproduced with permission from Morrow, A. G., Braunwald, E., Haller, J. A., and Sharp, E. H.: The left atrial pressure pulse in mitral valve disease. A correlation of pressures obtained by transbronchial puncture with the valvular lesion. Circulation 16: 399, 1957.)

to the valve in order to maintain cardiac output. Moreover, when blood flow is turbulent, as it is across stenotic valves, the pressure gradient is proportional to the square of the flow rate. Hence, precise estimation of the severity of valvular obstruction is dependent on the simultaneous measurement of the magnitude of the pressure gradient across the valve together with the flow rate. When valvular regurgitation coexists, the valve flow is the sum of the forward cardiac output and of the regurgitant flow. Since no accurate method for the assessment of the latter parameter is available, the hydraulic characterization of a valve which is both stenotic and regurgitant is not possible at present. However, since no significant valvular gradient exists normally, the measurement of pressures alone may be of value clinically simply in determining the presence or absence of stenosis.

Normal and Abnormal Pressure Pulses

Atrial Pressure Pulses

The normal atrial presure pulse has a characteristic configuration (Fig. 2). Atrial contraction commences 0.06 to 0.09 second after the onset of the P wave of the electrocardiogram. This mechanical event is reflected in the onset of the A wave of the atrial pressure pulse. During atrial relaxation atrial pressure declines. Shortly after the completion of inscription of the A wave, and 0.05 to 0.07 second after the onset of ventricular depolarization, as indicated by the beginning of the QRS complex of the electrocardiogram, the ventricles start to contract. This results first in closure and then in upward bulging of the atrioventricular valves. The latter phenomenon re-elevates atrial pressure, producing the C wave. During ventricular ejection, the atrioventricular ring descends, thereby increasing atrial capacity. This is reflected in an abrupt decline of atrial pressure, the *x* descent of the atrial pressure pulse. As ventricular systole progresses, the atria continue to fill from the venae cavae and pulmonary veins. This occurs in the presence of closed atrioventricular valves and both atrial volume and pressure increase. The *x* descent is therefore halted and reversed by a

sponsible for many of the symptoms of congestive heart failure.

Arterial Pressure Pulses

As might be anticipated, the contours of the central aortic and peripheral arterial pressure pulses are also modified in a characteristic manner by aortic valve deformities In patients with severe aortic stenosis, the velocity of left ventricular ejection is diminished and the central and peripheral arterial pressure pulse rise is abnormally slow The central aortic pressure pulse is characterized by several prominent oscillations on the anacrotic limb and by a delayed peak In the brachial artery pressure pulse, the anacrotic shoulder is more prominent and lower on the ascending limb than in the normal Both the peak systolic pressure and the dicrotic notch are delayed in timing In aortic regurgitation, the upstroke in both the central and peripheral pulses is quite steep, the catacrotic limb is collapsing and the incisural pressure is usually quite low in relation to the peak systolic pressure In the peripheral arterial pulse, the dicrotic notch is inconspicuous or absent In the presence of combined stenosis and regurgitation of the aortic valve, the central arterial pressure tracing generally presents a combination of the features described for each individual lesion The brachial artery pressure pulse frequently exhibits two distinct peaks, the so-called "pulsus bisferiens"

MEASUREMENT OF CARDIAC OUTPUT

The Fick Method

At the present time, two methods, the Fick and the indicator-dilution methods, may be employed for the measurement of cardiac output in man The Fick principle may be applied for the determination of blood flow to a variety of organs It may be stated as follows: The total uptake, or release, of a substance by an organ is the product of the blood flow to the organ and of the arteriovenous concentration of the substance under consideration For example, if the blood flow to the hind limb of a dog is 150 ml per minute and the arteriovenous difference in glucose concentration between the femoral artery and vein is 5 mg./100 ml., the total glucose uptake by the hind limb equals 150 ml per minute × 5 mg./100 ml. = 7 5 mg. per minute. Conversely, knowledge that the total glucose uptake by the hind limb is 7.5 mg per minute and that the femoral arteriovenous glucose difference is 5 mg./100 ml., makes possible the calculation of a hind limb blood flow of 150 ml per minute.

This principle may also be employed in the measurement of pulmonary blood flow, i e, the total cardiac output The patient's oxygen consumption is determined, as well as the mean arteriovenous oxygen difference for the entire body The diffusion of oxygen across the pulmonary alveolo-capillary membrane cannot be measured directly and it must be assumed to be equal to the oxygen uptake at the mouth during the period of measurement Since various tissues utilize varying proportions of the oxygen delivered to them, it is absolutely necessary to sample mixed venous blood in order to determine the arteriovenous oxygen difference. The sampling of truly mixed venous blood can be achieved either in the outflow tract of the right ventricle or in the pulmonary artery since streaming of blood takes place in the venae cavae and mixing is not even completed in the right atrium

The formula for the calculation of the cardiac output is:

$$\text{cardiac output (pulmonary blood flow)} = \frac{\text{total oxygen uptake}}{\text{arterio-mixed venous } O_2 \text{ difference}}$$

The determination of oxygen consumption must obviously be carried out with the subject in a "steady" or equilibrium state Ventilation and oxygen consumption must remain constant during the entire period of measurement During transient hypoventilation, the peripheral tissue oxygen utilization exceeds the uptake of oxygen at the mouth and thereby invalidates application of the Fick principle Furthermore, if during the course of the cardiac output determination the respiratory midposition is altered significantly, the oxygen uptake at the mouth is not equal to that which diffuses across the alveolar membrane, and again the cardiac output measurement is in error If the cardiac output changes during the two to three minutes

grees of mitral regurgitation, when the left atrium and ventricle may be functionally considered to be a single chamber, "ventricularization" of the left atrial pressure pulse occurs. Following ventricular relaxation, the distended atrium empties rapidly, resulting in a steep *y* descent. These alterations of the pressure pulse induced by valvular regurgitation are more prominent in the left than in the right atrium. During ventricular systole, each atrium may be considered to be part of a common chamber with the veins which it receives. The volume of the left atriopulmonary venous compartment is much smaller than of the corresponding right atrio-vena caval chamber. In addition, it has been demonstrated that the right atrium is more distensible than the left. For these reasons, the regurgitation of a given volume of blood will result in a larger pressure change, *i.e., a greater elevation of the V wave, in the* left than in the right atrium. The atrial pressure pulse has been found to be of considerably greater value in the clinical detection of mitral than of tricuspid regurgitation.

When stenosis of the mitral or tricuspid valves is present, the atrial pressure is also modified in a characteristic manner. The obstruction to atrial emptying results in an elevation of mean atrial pressure. Patients with tricuspid stenosis may exhibit enormous right atrial A waves with peaks which approach or even exceed the magnitude of the *right* ventricular systolic pressure. Prominence of the left atrial A wave is less frequently observed in patients with mitral stenosis. The most characteristic modification of the atrial pressure pulse in patients with mitral and tricuspid stenosis, however, occurs during ventricular diastole. The normal rapid emptying of the atria and filling of the ventricles which occurs after the peak of the V wave is prevented. The atrial pressure declines slowly during early diastole, i.e., the *y* descent is gradual and prolonged (Fig. 3). The presence of obstruction to atrial emptying prevents adequate ventricular filling and in mid-diastole both the ventricular and atrial pressures continue to fall; diastasis is thus eliminated. It has been observed that patients with elevated left atrial pressures in whom the left atrial pressure decline during the first 0.10 second of the *y* descent is less than 40 per cent of the mean left atrial pressure, and with diastasis absent have had significant mitral stenosis at operation.

Ventricular Pressure Pulses

The ventricular pressure pulse is modified in a characteristic manner by severe stenosis of the semilunar valves. In this circumstance, the affected ventricle contracts in a more nearly isometric manner than normal, and the pressure tracing exhibits a peaked summit during midsystole, instead of the normal plateau. The duration of the ventricular systolic pressure elevation is prolonged by severe obstruction to ventricular outflow. In patients with severe mitral regurgitation, an abnormal abrupt decline in left ventricular pressure takes place at the termination of ventricular systole.

In conditions in which diastolic cardiac distensibility is diminished, such as constrictive pericarditis, endocardial fibroelastosis or amyloid disease of the heart, a characteristic modification of the ventricular pressure pulse also takes place. The early, rapid ventricular filling phase is abruptly terminated as ventricular enlargement suddenly stops. Further ventricular inflow is accompanied by a marked elevation of ventricular pressure in mid-diastole which persists up to the next ventricular systole. The resulting contour has been described as an early *diastolic "dip" followed by a diastolic plateau*.

In the presence of congestive heart failure, myocardial contractility is depressed. One of the first responses to depressed myocardial contractility is ventricular dilatation during diastole, a compensatory mechanism which tends to maintain the force of ventricular contraction. The rise in ventricular end diastolic volume is accompanied by an elevation of ventricular end diastolic pressure. For this reason, the level of the ventricular end diastolic pressure is an important index of ventricular function. In the absence of pericardial or endocardial disease, an abnormal elevation of ventricular end diastolic pressure signifies impairment of myocardial contractility, i.e., ventricular failure. This elevation of end diastolic pressure in turn raises the level of the corresponding atrial and venous pressures and is re-

pling twice before other portions have passed the first time If the recirculating indicator is not recognized, the indicator dilution curve would encompass an abnormally large area and therefore would yield a falsely low cardiac output However, since the indicator mixes completely in the central circulation, its rate of washout at any moment is directly proportional to the quantity remaining in the central circulatory bed. When the time-concentration curve is plotted on semilogarithmic paper, the descending limb forms a straight line (Fig. 4). Departure from this straight line may occur and results from recirculating indicator The disturbing influence of this recirculating indicator may therefore be eliminated by assuming a logarithmic washout for the indicator for the entire descending limb of the indicator-dilution curve.

Distortion of the primary dilution curve by recirculating indicator is more prominent under three circumstances: (1) an increase in the volume of blood between the injection and sampling sites as may occur in congestive heart failure, (2) slowing of the circulation as in heart failure or shock and (3) the presence of a central circulatory left-to-right shunt

The indicator most commonly employed for the determination of cardiac output is Evan's blue dye (T 1824) However, more recently indigo carmine, tricarbocyanine, I_{131} tagged albumin, hypertonic saline, and cold saline have been employed When a colored dye is employed its concentration may be determined spectrophotometrically in samples obtained from a peripheral artery at one to two second intervals Alternatively, the time-concentration curve may be directly inscribed by means of a continuous recording cuvette densitometer or cuvette oximeter.

An estimate of stroke volume may also be achieved by various analyses of the central or peripheral arterial pressure pulse The ballistocardiogram has been similarly employed for the measurement of stroke volume. Both of these approaches are to a large degree empiric and yield approximate values at best They are useful, however, in experimental or clinical circumstances in which it is of importance to

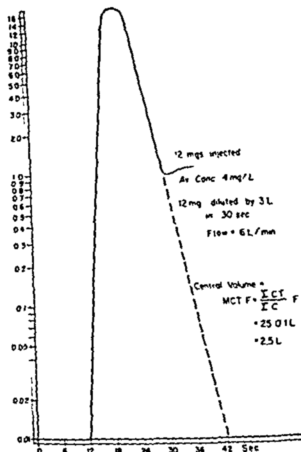


Fig. 4—Indicator-dilution curve replotted on semilogarithmic paper The methods for calculating cardiac output and central blood volume are indicated The broken line represents the extrapolation of the descending limb because of recirculating indicator (Reproduced with permission from Hamilton, W F The physiology of the cardiac output Circulation *8* 527, 1953)

follow directional changes of stroke volume, but in which absolute values are not required

The cardiac output is quite inconstant, its level at any instant dependent not only on the adequacy of myocardial function, but also on the metabolic requirements of the organism, on the total blood volume, on the distribution of blood between thorax and periphery, on arteriolar and venous tone, as well as on a variety of neural and humoral influences. For this reason, a single, isolated measurement of the cardiac output has little physiologic or clinical significance and is of little value in assessing circulatory adequacy. However, the level of the cardiac output becomes meaningful when it is measured in the resting, basal state. Under

usually required for the cardiac output determination, and if blood is sampled from the pulmonary and systemic artery at a constant rate, further errors are introduced Minor errors result from small right-to-left intrapulmonary shunts and from the thebesian veins which drain into the left side of the heart Both of these types of shunts depress the oxygen content of the systemic arterial bed to slightly below that in the pulmonary veins

In practice, many of the difficulties inherent in the proper application of the Fick principle can be minimized A number of criteria are available to determine whether the subject is in a basal, steady state at the time of the determination of the cardiac output The minute ventilation, oxygen consumption and heart rate are excellent guides to the presence of the basal state. Perhaps the most sensitive index of the "steady" or equilibrium state is the respiratory quotient, i.e , the ratio of CO_2 production to O_2 consumption (R Q.). In the postabsorptive state, the R Q. should range between 0 70 and 0 90 In the presence of hyperventilation, when the amount of CO_2 exhaled exceeds the true peripheral tissue CO_2 production, an abnormal elevation of the R.Q exists This is frequently observed in patients who are anxious and unfamiliar with the complex apparatus in the cardiac catheterization laboratory It may frequently be avoided if the patient is brought to the laboratory prior to the catheterization and is familiarized with the staff, room and the equipment The procedure which will be followed should be explained carefully and a trial measurement of oxygen consumption carried out.

When the Fick principle is applied during exercise, hyperventilation and an abnormally elevated R Q are often noted during the first few minutes For this reason, it is necessary to continue a steady rate of exercise for approximately seven minutes before cardiac output measurements are begun. In patients with left-to-right shunts, well oxygenated blood from the left side of the heart shunts across the defect and mixes with the poorly oxygenated blood in the right side of the heart. The pulmonary arteriovenous oxygen difference is therefore markedly narrowed in the presence of a moderate or large shunt Under these circumstances, the Fick method cannot be relied on for an accurate determination of pulmonary blood flow because of the technical errors inherent in the determination of the blood oxygen content

Indicator-Dilution Method

The indicator-dilution method for the measurement of cardiac output is based on the following principle: A known quantity of an indicator substance is rapidly injected into a peripheral vein, the right heart or pulmonary artery In the course of its first circulation, it becomes diluted into a progressively greater volume of blood The changing concentration of the indicator in a peripheral artery is then determined, yielding a time-concentration curve The calculation of the average concentration of the indicator during the inscription of the curve yields the total volume of blood into which the indicator has become diluted during its passage from the site of injection to the site of sampling. The time-concentration curve also indicates the time required for this volume of blood to pass the site of sampling. thus permitting calculation of the cardiac output In the example illustrated in FIGURE 4, the total quantity of dye injected was 12 mg of Evan's blue Since the mean concentration of dye in the arterial blood during the inscription of the primary curve was 4 mg /L , the indicator became diluted in the following manner: 12 mg /4 mg /L = 3.0 L. The indicator, diluted in 3 0 L of blood, appeared at the sampling site 12 seconds after injection and disappeared 30 seconds later The flow rate then equaled 3 L /30 seconds or 6 0 L per minute The effectively circulating blood volume between the site of injection and of sampling may also be calculated from indicator-dilution curves by determining the product of the cardiac output and the mean circulation time between the sites of injection and sampling

The principle of the indicator-dilution technic is based on the time-concentration characteristics of the indicator during its *first* passage from the site of injection to the site of sampling Because of the presence of circulatory paths of widely varying lengths, it is possible for portions of the indicator to pass the site of sam-

circulation Upon its arrival in the left side of the heart a portion takes the normal circulatory path across the aortic valve and thence to the periphery The remainder is shunted back to the right heart and through the pulmonary circulation Upon its return to the left heart a fraction is again shunted from left to right Consequently, the resultant dilution curve obtained from a systemic artery has a low peak concentration and an abnormally prolonged descending limb Injections into the right side of the heart are therefore of value in the detection of such shunts Varying the site of injection has little influence on the general configuration of the curve and is not of value in the localization of left-to-right cardiac shunts

In contrast, the injections of indicator into the left side of the heart and into the aorta are of considerable value in the localization of left-to-right shunts When the injection is made distal to the origin of a left-to-right shunt, all of the dye follows the normal circulatory path across the aortic valve and into the peripheral circulation The resultant dilution curve has a steep ascent and slightly slower descent, but returns to the base line before the appearance of recirculating indicator However, when the injection is made proximal to the origin of a left-to-right shunt, only a portion of the indicator takes the normal circulatory path The remainder is shunted across the defect and through the pulmonary circulation. The late appearance of this portion of the indicator in the peripheral artery abruptly interrupts the descending limb of the normal curve and results in either a secondary peak or in an abrupt change in the slope of the descending limb.

Thus, in a patient with an atrial septal defect the injection into the left atrium results in an abnormal curve, while injection into the left ventricle results in a normal curve (Fig 5) This application of the indicator-dilution technic has been found to be particularly useful in the preoperative study of patients with atrial septal defects. An abnormal curve following left ventricular injection in such patients always indicates the presence of a complicating lesion, such as mitral regurgitation or

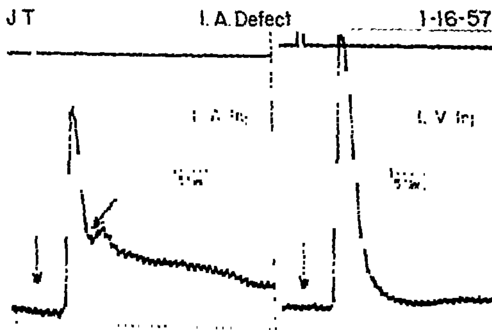


Fig 5.—Indicator-dilution curves recorded from a peripheral artery following injection of indigo-carmine into the left atrium (*left*) and left ventricle (*right*) in a patient with an uncomplicated atrial septal defect Vertical arrows indicate time of injection Oblique arrow on curve following left atrial injection indicates appearance of indicator which had passed across defect (Reproduced with permission from Braunwald, E, Tanenbaum, H L, and Morrow, A. G: Localization of left-to-right shunts by dye-dilution curves following injections into the left side of the heart and into the aorta Am J Med 24: 203, 1958)

these circumstances, the variability of extraneous influences is reduced and it is possible to compare a particular individual with others, provided similar technics are employed in all determinations Furthermore, when the cardiac output is first measured in the basal state, the hemodynamic effects of a variety of interventions may be studied The most important of these is the response of the cardiac output to the stress of exercise In normal man, the cardiac output rises at least 600 ml per minute for every 100 ml per minute rise in oxygen consumption.

If cardiac function is assessed by a consideration of the adequacy with which the heart supplies the peripheral tissues with oxygen, then the systemic arterio-mixed venous oxygen difference becomes an important and meaningful index Regardless of the absolute level of the cardiac output, an abnormally wide arteriovenous oxygen difference signifies that the heart fails to make adequate quantities of blood available to the organism

Indicator-Dilution Curves in Cardiovascular Diagnosis

In recent years, continuously recorded indicator-dilution curves have been found to be of considerable value in the recognition and localization of a variety of cardiac shunts as well as in the detection of valvular regurgitation

Right-to-Left Shunts

Following injection into the right heart proximal to the origin of a right-to-left shunt, an indicator follows two circulatory paths A portion of the indicator takes the normal route through the pulmonary circulation, thence through the left side of the heart, and into the systemic arterial bed This fraction of the indicator produces the normal component of the resultant dilution curve. The remainder of the indicator follows the blood through its abnormal circulatory path, i e , it is shunted from the right to the left side of the heart, bypasses the pulmonary circulation and therefore appears abnormally early in the systemic arteries. This fraction of the dye is responsible for the abnormal component of the resultant dilution curve, i e., it results in an abnormally early appearance time and an early peak preceding the normal component of the dilution curve. Either a double-peaked contour or an early appearance time followed by an abrupt change in the slope of the ascending limb results from the two circulatory paths traversed by the indicator The selective injection of indicator dye into the right atrium, right ventricle and pulmonary artery makes the precise localization of the origin of right-to-left shunts possible For example, in a patient with pulmonary stenosis with a right-to-left shunt through a patent foramen ovale, injection into the right atrium results in an abnormal circulatory path A normal dye curve results from right ventricular injection In contrast, in patients with the tetralogy of Fallot, dye injections into both the right atrium and right ventricle result in abnormal curves with an early appearance time. In such patients, injections into the pulmonary artery result in normal curves The injection of an indicator into a peripheral vein serves as a valuable screening test in the study of patients with cyanosis of central origin The abnormal curves described above are obtained in patients in whom the cyanosis is secondary to a cardiac right-to-left shunt However, in patients with intrapulmonary shunting, i e , with areas of the lung which are well perfused but inadequately ventilated, a normally shaped dilution curve results In the former patients, the presence of the right-to-left shunt shortens the circulatory path, while in the latter this does not take place In patients with arterial unsaturation, the use of blue dyes is not always satisfactory since the spectral absorption properties of reduced hemoglobin resemble those of the blue dyes The recent introduction of tricarbocyanine dye obviates this difficulty since the maximal light absorption of this dye occurs at the wavelength at which the light transmission of reduced and oxygenated hemoglobin are identical

Left-to-Right Shunts

When indicator is injected into a peripheral vein, right side of the heart or pulmonary artery of a patient with a left-to-right cardiac shunt, it is dispersed into the abnormally large volume of blood which traverses the pulmonary

patients with chronic pulmonary disease and various types of cardio-circulatory disease J Clin. Invest 25: 643, 1946
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an associated ventricular septal defect. Indicator-dilution curves have also been of considerable value in determining the drainage path of pulmonary veins entered during the course of right heart catheterization. The dilution curve obtained from a systemic artery following the injection of dye into such a vein is characterized by an early appearance time and a contour which resembles that following left atrial injection if the pulmonary vein in question drains normally into the left atrium Conversely, following injection of indicator into a pulmonary vein which drains into the right atrium, the dilution curve has an appearance time which is prolonged and a contour resembling one which follows right atrial injection

A method particularly suited for the detection of small left-to-right shunts consists of the injection of indicator dye into the pulmonary artery, while sampling from another catheter in the right atrium or right ventricle The rapid appearance of dye in the right side of the heart establishes the presence of a left-to-right shunt, while the particular chamber in which the dye appears indicates the site of entry of the shunt

Valvular Regurgitation

Indicator dilution curves have also afforded means for the recognition of valvular regurgitation When a valve which regurgitates a significant volume of blood is interposed between the sites of injection and sampling of the indicator, the curve characteristically exhibits a depressed peak, a slight prolongation of the ascending limb, a more striking prolongation of the descending limb and disappearance of the normal recirculation peak Even careful analysis of such curves has not provided a precise method for the measurement of regurgitant flow. When the injection is made in the chamber just downstream to the regurgitant valve, the descending limb is also relatively prolonged in comparison to the ascending limb. However, a normal contour is obtained when the indicator is introduced into a chamber distal to the competent valve just downstream to the regurgitant valve. In this manner, the site of valvular regurgitation may be localized. Regurgitation can also be recognized by the detection of dye in the chamber proximal to the injection site. For example, when dye injected into the pulmonary artery through the distal lumen of a cardiac catheter immediately appears in blood sampled from the right ventricle through the proximal lumen of the catheter, the diagonsis of pulmonary regurgitation is confirmed Utilizing simultaneous left ventricular catheterization and left atrial puncture, mitral regurgitation may be detected in a similar manner Some investigators have used this approach for the quantification of mitral regurgitation However, the validity of such methods remains to be demonstrated. Finally, aortic regurgitant flow has been detected by the injection of indicator dye at various levels in the descending aorta through a catheter introduced percutaneously through the femoral artery The lowest point in the descending aorta from which injected dye regurgitates back to the ascending aorta and subsequently perfuses the right ear may be determined by means of an oximeter placed on the right ear. This method has also afforded estimations of the magnitude of aortic reflux.

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Cardiovascular Dynamics–Technics for Indirect Measurements

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BALLISTOCARDIOGRAPHY

A CLEAR perspective of ballistocardiography has been difficult to achieve. This has been due in part to the many different technics which have been used in recording the motions of the body. The type of ballistocardiographic complex obtained depends on the technic used and conclusions obtained from one method cannot be applied to data obtained by other procedures. Confusion has existed as to which method is best from a physical sense or more useful clinically. In the last few years the physical principles involved in recording body motion have been studied and delineated by von Wittern,[25] Noordergraaf,[11] Burger,[4] Talbot,[24] and others.[13] As most of the clinical ballistocardiographic investigation has been done with technics which have now been shown to introduce gross distortion of the reaction of the body to circulatory events, much of the available literature has to be viewed with skepticism. Final evaluation of the over-all clinical usefulness of the ballistocardiogram must await further studies with improved technic.

It is now generally agreed that the ultra low-frequency or aperiodic systems are the best methods by which the reaction of the body to circulatory events can be recorded accurately without significant artifacts. Certain definitions may be helpful in the present considerations:

1. The *frequency* of a motion is the vibration rate (movement back and forth) of an object. This is usually expressed as cycles per second (cps).

2. *Forcing frequency* is the frequency of the internal vibrations as generated by the cardiovascular forces which are responsible for the ballistocardiogram.

3. *Natural frequency* is the rate a body or object oscillates after being first set in motion. For instance, the C-tuning fork, when struck, vibrates 256 times a second.

4. *Phase shift* is the shift in degrees away from the original signal. For instance, velocity is 90 degrees out of phase from displacement, and acceleration is 90 degrees out of phase from velocity. Considering a sine wave, the peak velocity occurs at the midportion (position) in the displacement wave, and the peak acceleration which is 180 degrees out of phase with acceleration occurs at the very start of the displacement wave.

High-frequency systems. The Starr table is the classic example of a high frequency system and much of the ballistocardiographic experience has been obtained with this technic. The platform on which the patient lies is fairly heavy, and in addition the natural frequency of the bed is about 10 cps unloaded and 4 or 5 cps with a patient on the platform. As a result, when the displacement of the bed is recorded, the deflections are actually proportional to the acceleration of the circulatory mass for frequencies below 3 to 4 cps. The forcing frequencies which are in the range of the natural frequency of the bed (3 to 6 cps) are grossly exaggerated in amplitude. Forcing frequencies above 4 to 6 cps are recorded with a distinct phase shift as well as with a substantial decrease in amplitude. Thus, the resulting trace is not linear with respect to the forcing frequencies and is inaccurate both in amplitude and timing. It is true that the major forcing frequencies of cardiovascular motion probably are relatively low and therefore the traces as recorded on the high-frequency table may be reasonably accurate for the study of I and the J complexes. Although important contributions

have been made with this technic, the unsolved technical problems limit the general application

Direct body technics. The direct body methods are generally unsatisfactory, as the records tend to distort the cardiovascular forces [13] The most widely used technic provides a record of body motion, using a platform resting on the shins of the patient. This motion can be recorded as displacement, velocity or acceleration It should be emphasized, however, that even though sensing units are employed the resultant curves do not necessarily represent the true displacement, velocity or acceleration of the corresponding events of the heart and circulation This is due to two factors: (1) A distortion of the forces that lie close to the natural frequency of the body and (2) difficulty in coupling the shin bar to the patient, resulting in some relative motion between the patient and the shin board The difficulties in the latter largely have been eliminated by Smith[17] who pointed out the necessity of having an extremely light shin platform The natural frequency of the body, supine on a flat surface, usually is somewhere between 3 and 6 cps which unfortunately is in the middle of the forcing frequencies generated by the heart and circulation Consequently, any cardiovascular force which has the same frequency as the natural body frequency is considerably distorted in amplitude with as much as 100 per cent or greater overshoot due to reasonance There is always a shift in phase above and below the natural body frequency so that all forces below will be recorded 180 degrees out of phase with respect to the forcing frequencies Thus, the records from any direct technic do not provide a linear representation with respect to phase and amplitude of the forcing frequencies of the circulatory system The natural body frequency can be elevated by placing the patient on a sand or putty surface [26] This decreases the relative motion between the body and the surface on which the patient lies and somewhat improves the linearity and fidelity of the records Further limiting body motion by packing sand bags on the feet and shoulders also aids in elevating the natural frequency of the body Even with these procedures, however, the natural frequency rarely is raised to more than 10 cps [24] Although the forcing frequencies below 10 cps will be fairly accurately recorded (the displacement is proportional to acceleration) using these procedures, there is distortion at 10 cps with a shift in phase and amplitude above this point. It is now generally believed that the forcing frequencies of the circulatory system may go as high as 30 to 40 cps. Obviously, the technic of restraining body motion is not sufficient to elevate the natural frequency of the body enough for recording an accurate ballistocardiogram Although those who have had extensive experience with the direct technic have been able to correlate the clinical state of patients with the ballistocardiographic records, the technical difficulties as presented seriously limit the above-all usefulness of the technic.

Low-frequency critically damped technic. This method was introduced by Nickerson and consists of a rather heavy platform which is critically damped so that its natural frequency is approximately 1 cps. The critical damping virtually eliminates the diastolic portion of the complex There are also distortions as to phase and amplitude, though less so than in the two previous technics described. The recorded displacement is proportional to the displacement of the circulatory mass for events having a frequency above 2 to 3 cps.

Ultra low-frequency technic The physical principles of the ultra low-frequency technic have been well defined[4, 11, 23, 25] as the only satisfactory method for recording accurately the forcing frequencies of the cardiovascular system There are several types of bed suspension which can be used These include a platform suspended by wires from the ceiling similar to that originally used by Henderson[8] (one of the first systems developed for recording the ballistocardiograms), a horizontal pendulum-like suspension,[15] a bed mounted on roller bearings,[9] a platform floating on mercury[22] and more recently a bed suspended on the principle of an inverted pendulum [16] Certain precautions are necessary in setting up these systems and when followed the traces recorded from any suspension are essentially the same The principles which must be adhered to are: (1) The plat-

form must be as light as possible (less than 12 pounds) to obtain sufficient coupling between the body and the platform. Reducing the weight of the platform decreases the relative motion between the body and the platform and therefore produces less distortion of the cardiovascular forces It is possible that a slightly heavier bed may be used if other means are used to increase the coupling of the patient to the platform, such as shoulder straps (2) The natural frequency of the system must be as low as possible (at least below 0.3 cps) in order to separate the natural frequency of the platform from the forcing frequencies Thus, all frequencies above the natural frequency will be recorded accurately with respect to amplitude and phase With a system of this type the body motion following the cardiovascular forces then can be sensed accurately as displacement, velocity or acceleration. (3) To record a ballistocardiogram of good fidelity some care must be taken in selecting transducers by which the motion of the platform is sensed Because the accelerations of the platform are relatively small, a very sensitive accelerometer and one which is linear over a wide range of frequency, probably up to 35 cps, must be

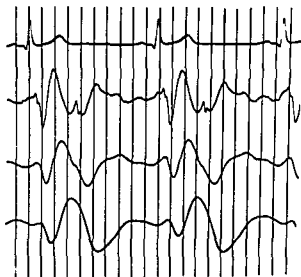


Fig 1—A normal ultra low-frequency ballistocardiogram The top trace is a Lead II electrocardiogram The second is the acceleration trace, the third, the velocity, and the fourth, displacement The time lines are 10 second apart The velocity trace is actually the first integral of the acceleration trace and the displacement, the first integral of the velocity trace

used Accelerometers are usually rated by the manufacturer as to their natural frequency. This does not necessarily indicate that the accelerometer is capable of sensing all frequencies up to that point, since the accelerometer itself *tends to have distortion around its own natural* frequency Thus, to insure fidelity of recording (for 1 to 35 cps) one should choose an accelerometer with a natural frequency at least as high as 50 cps.* There are also problems in recording velocity. Some commercial velocity pickups have filtering circuits which attenuate the higher frequencies We have found it best to integrate electrically the acceleration signal to velocity

Because respiration sets up very low-frequency movements of the platform, displacement records are the most difficult to obtain from an ultra low-frequency system The wide swings in displacement due to breathing make it necessary to obtain the records during a period of held respiration Although displacement, velocity and acceleration records represent only different functions of the same motion, there appears to be certain information that can be obtained from each of these traces that is not readily apparent from a single trace Figure 1 is an example of head-foot acceleration, velocity and displacement records from an ultra low-frequency system

Genesis of the ballistocardiogram. The mechanisms of production of the various waves in the ballistocardiogram are still basically unknown However, the classic work of Starr with simulated systole at necropsy offers the best evidence as to the genesis of some of the movements of the ballistocardiogram. Starr has shown very convincingly with simulated ejection that the initial acceleration of blood produces a recoil force corresponding to the I wave of the ballistocardiogram [21] This is followed by *the impact of blood in the aorta* resulting in the J wave Evidence that the K wave is related to deceleration of the blood in the descending aorta has been obtained principally from the study of ballistocardiograms from patients with coarctation of the aorta.[2, 10] *Thus,*

* We have found the accelerometers made by Northam Electronics, Inc, 2120 North Lake Avenue, Altadena, California, satisfactory

the ballistocardiogram has been related almost entirely to the forces associated with the flow of blood in the arterial tree

Recent evidence from dog experiments suggests the possibility that forces associated with myocardial contraction *per se* may be important in the genesis of the ballistocardiogram, as the entire complex can be noted during a time when there has been a complete cessation of blood flow and with an empty heart.[7] Although there is still some doubt as to the actual significance of these findings, it is obvious that the genesis of the ballistocardiogram is extremely complex and may be composed of myocardial forces as well as forces due to the contraction of the ventricular muscle itself In fact, all forces actually originate in the myocardium The movements due to atrial contraction occasionally may be superimposed on the H wave, and the separation into a distinct ventricular H component may not be possible However, the H wave is not entirely due to auricular forces as it is present in patients with atrial fibrillation and complete heart block

The genesis of the ultra low-frequency ballistocardiogram has been considered from a somewhat different viewpoint by Noordergraaf[11] and Burger[4] who have suggested that the forces result from the changes in the relative center of *gravity of the body* due to the movements of blood within the vascular bed Recently, this concept has been further considered, the waves being correlated with physiologic events [16] In general, the events remain the same but the approach differs.

Genesis of the abnormal ballistocardiogram is even more obscure than the normal, and again the most significant experimental studies were made by Starr during simulated systole at necropsy [19] He found by changing the padding on the mallet that the rate of ejection into the arterial tree was altered This changed the configuration of the ballistocardiographic pattern and many of the abnormal forms of ballistocardiographic complexes resulted

It is quite obvious that the ballistocardiogram is a complex wave form generated by forces produced by many superimposed events The resultant pattern represents the summation of many forces and will never be clearly defined in terms of one or two isolated events

Respiratory variations The ballistocardiographic variation in amplitude and configuration during the respiratory cycle is well appreciated. At the present time, the reasons for these respiratory variations are still not entirely clear. The complexes usually become larger during inspiration than during expiration; however, if one accurately correlates the amplitude of the complexes through the respiratory cycle, occasional complexes during expiration may be as high or higher in amplitude than those occurring in inspiration Nevertheless, the inspiratory complexes are generally larger than those during expiration These variations have been attributed to several factors. Inspiration favors an increase in blood flow into the right ventricle and into the pulmonary artery Therefore, the increase in the ballistocardiographic amplitude during inspiration has been assumed to be due to an increase in forces from the right side of the heart and the pulmonary artery This would imply that the forces associated with blood flow into the pulmonary artery dominate the ballistocardiographic records Recent analysis by Noordergraaf[12] has failed to confirm this, and the contribution of the right side of the circulation is apparently much smaller than that from the left An additional explanation has been based on the changes in heart position during respiration The heart becomes more vertical during inspiration which would tend to align the overall axis in a more head-foot direction, thus increasing the forces during inspiration However, studies made by changing the recording axis of the platform fail to confirm this.[20] In addition, when one records both lateral and head-foot forces simultaneously, the traces often will show an increase in amplitude of both the head-foot and lateral axes, indicating the respiratory variation cannot be attributed solely to heart position Thus, the causes for the respiratory variations are at present unknown, however, one possible explanation remains for which there is little experimental evidence available The variations may represent changes in function of the left ventricle due to respiratory reflexes resulting in varia-

tions in blood velocities or rates of ejection and blood flow during these periods. Neurogenic reflexes which alter contractility of the left ventricle may be the explanation

Method of analysis Ballistocardiograms usually are analyzed as to the degree of abnormality by visual inspection of the traces This is an empiric approach and its reliability depends on the experience of the physician reading the traces If this proves to be the only method by which ballistocardiograms can be interpreted, then this considerably limits the over-all usefulness of the technic Another method of analysis that has been applied to the low-frequency and high-frequency traces is based on rating the degree of abnormality as occurs during respiration [1, 3, 5] Traces which are totally chaotic are given a grade of 4, those with the smaller complexes, e g , less than 40 per cent of the largest complexes noted during inspiration, are graded as one Grades 2 and 3 represent the intermediate differences As mentioned previously, this type of analysis has been applied primarily to the traces from the high-frequency bed There is evidence that this evaluation may be of value clinically, with some merit even when applied to the ultra low-frequency traces However, its ultimate usefulness will depend on a better definition of the respiratory variations

An analysis of the time measurements of the various ballistocardiographic waves may prove useful in the correlation of various known cardiovascular events to points on the complex [14] It has been found in patients with right ventricular hypertrophy that there is often an exaggeration of the first portion of the HI downstroke Also, in coronary artery disease there may be a delay in the J peak The consistency of these findings in disease states has not been fully defined

The amplitude records derived from the ultra low-frequency technic can be measured and converted, with reasonable accuracy to units of acceleration or force. These measurements are also subject to limitations, since the force (in dynes) may not necessarily represent true cardiovascular force, for the following reasons: (1) The available beds usually provide records in one or two axes, and only the portion of the total force in the head-foot axis is registered. (2) Amplitude measurements represent only peak forces. A patient may exhibit a complex characterized as a decrease in peak force, however, it should be mentioned that the force may have been active over a long period of time This may be comparable to a heart which has a higher peak force but of shorter duration It is possible that the phenomenon is the reflection of a significant though undefined physiologic mechanism. Since the ballistocardiogram probably represents a summation of many forces taking place simultaneously in all directions, it is conceivable that the heart generates simultaneous forces, in opposite directions, which would completely neutralize each other In addition, amplitude measurements alone may have limited usefulness since preliminary study indicates that the accelerations or forces in a group of patients with coronary artery disease overlap the normal range [6] Thus, other approaches need to be developed Similar criticism can be applied to the velocity and even displacement records It is perhaps fair to conclude at the present time there is no proved, reliable method for analyzing ballistocardiograms

Application of Ballistocardiograms to Cardiovascular Physiology and Disease

Experience with the ultra low-frequency systems has been so limited that the clinical value of the ballistocardiogram cannot be estimated at the present time There are several reasons, however, why this technic is of interest (1) The original study by Starr[18] as to the prediction of coronary artery disease by the ballistocardiogram is still extremely intriguing, even though the data were obtained on the high-frequency system (2) The ballistocardiogram is an exceedingly delicate measurement of certain ill defined cardiovascular functions, and it is possible that abnormalities may appear in the recordings before onset of cardiovascular derangement It is quite probable that there will never be any specific etiologic, diagnostic potentialities of the ballistocardiogram In contrast, theoretical considerations and experimental evidence suggest that the ballistocardiogram may be related primarily to the

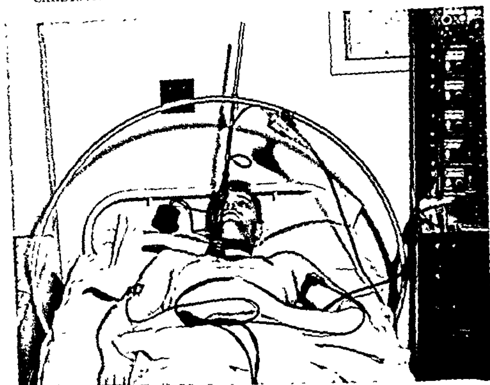


FIG 2 — A photograph of the kinetocardiographic apparatus

integrity of cardiovascular function Since there are no simple methods available to determine how well the heart is working as a "pump," the ballistocardiogram, if related to heart function, may be of considerable importance It appears that the over-all potential usefulness of the technic will lie in the evaluation of cardiovascular mechanical function rather than diagnosis per se

KINETOCARDIOGRAPHY

The kinetocardiogram is a name given to the records of ultra low-frequency precordial movements recorded by a technic different from that previously used for apex cardiograms The differences between the two types of traces will be discussed subsequently The kinetocardiographic records are considered as a graphic representation of precordial movements elicited at the bedside The method used for recording the precordial movements employs a flexible metal bellows connected by means of a rubber tubing to a pressure sensitive transducer [34, 35]

FIGURE 2 is a photograph of the apparatus The probe end of the bellows is approximately 7 mm in diameter The exact size is unimportant, as long as the contact point is relatively small The tube attached to the transducer should be kept under 2 feet in length, thus assuring that resonance frequency within the system is sufficiently high to prevent distortion Two types of transducers have been used extensively, one is the piezo-electric* transducer and the other a P5a low-pressure Statham strain-gauge pressure transducer. Both of these yield displacement records of precordial motion As the frequencies of these movements are for the major part below 20 cps, both transducers have an adequate response Theoretically, the piezo-electric transducer is less desirable since it has a finite time constant and may permit an artifactual decay in the trace if the signal is somewhat sustained This occurs only at very low frequencies (below 1 cps) and therefore is a minor objection Care must be taken in selection of the piezo-electric transducer in order to insure that its response is linear With the two types of transducer mentioned, the traces obtained are

* Manufactured by the Cambridge Instrument Company Inc, New York 17, New York

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Experience with the ultra low-frequency systems has been so limited that the clinical value of the ballistocardiogram cannot be estimated at the present time There are several reasons, however, why this technic is of interest. (1) The original study by Starr[18] as to the prediction of coronary artery disease by the ballistocardiogram is still extremely intriguing, even though the data were obtained on the high-frequency system (2) The ballistocardiogram is an exceedingly delicate measurement of certain ill defined cardiovascular functions, and it is possible that abnormalities may appear in the recordings before onset of cardiovascular derangement It is quite probable that there will never be any specific etiologic, diagnostic potentialities of the ballistocardiogram In contrast, theoretical considerations and experimental evidence suggest that the ballistocardiogram may be related primarily to the

of the entire heart movements, the movements of the heart just beneath the probe contribute more to the trace from that point

The kinetocardiogram differs from the well known apex cardiogram in representing the absolute motion at a given point rather than relative interspace motion Most of the other methods used for recording low-frequency precordial motion employ transducers or pickup devices which rest directly on the chest wall All of these have the same inherent difficulty, since the resultant trace represents the differential motion between the point or points which rest on the chest and the sensing probe or diaphragm Therefore, the traces are affected considerably by the degree of relative interspace motion It has been found that the recorded trace from a sensing device that rests on the chest can be constructed by combining the absolute motions of the resting point with that from the sensing point [38] The fact that apex cardiograms represent a differential motion between two or more points dependent on the pickup device makes the traces appear to be more variable than those recorded with the kinetocardiographic technic Rocking or heaving motions of the precordium with little interspace motion are poorly registered in apex cardiograms. In addition, the width of the interspace may also cause some variation in the records. Therefore, it is quite understandable that apex cardiograms are not consistent, as pointed out by Wiggers a number of years ago [43] *There are other advantages* in recording precordial motion from a reference point outside the body These traces are a better graphic representation of the heart movements that can be palpated at the bedside

It is important to note that the superiority of the kinetocardiographic traces in regard to their clinical usefulness over those of relative interspace motion (apex cardiograms) has not been definitely established, as there are no comparative studies. However, the fact that the kinetocardiographic traces are reproducible, and records from different normal subjects similar in most respects (provided the tracing is recorded *from a comparable point* on the precordium) there is offered some advantage over the apex cardiograms It is possible that more information concerning cardiovascular physiology and disease states can be obtained by *recording precordial* motion with both technics

Low-frequency movements of the precordium *obviously can be registered in a number* of ways other than displacement, such as velocity or acceleration; however, such traces are exceedingly complex Thus, the present discussion is concerned only with the displacement records

The genesis of the low-frequency precordial movements Low-frequency precordial movements are related to several general factors [31, 35] (1) The molar motions and shape changes of the heart, (2) volume changes of the heart and/or interthoracic volume changes and (3) possibly impacts and forces due to movement of blood within the heart and great vessels

FIGURE 3 is a typical, normal kinetocardiogram for reference It is considered under three separate phases (1) The pre-ejection phase which begins with the onset of the QRS complex and ends with the onset of ejection as determined by the upstroke in the carotid pulse, (2) the ejection phase, as determined by the upstroke in the carotid pulse to the carotid incisural notch and lastly (3) the diastolic phase to the remaining portion of the cardiac cycle.

There are many small deflections noted in the traces from the various points, and studies are under way to define in detail the various movements of the kinetocardiogram; however, for descriptive purposes most of the small movements are ignored and only the general characteristics will be discussed. Approximately 04 second after the onset of the QRS complex there may be an abrupt outward movement most marked in the K_1 area, but often represented over the entire precordium. This can usually be differentiated from the movements due to atrial contraction since it begins after the onset of the QRS complex and is rather abrupt and outward in type. The phenomenon is attributed primarily to right ventricular activity and may be due to an anterior motion of the heart. The best evidence for this is obtained from patients with right ventricular

almost identical, and in only rare instances (in patients with very slow heart rates) does decay become a problem.

Other types of displacement sensing probes and transducers have been employed, all of which yield traces which are almost identical to those obtained with the bellows Records also have been obtained with a photocell in which there was no contact between the point of the chest wall being recorded and the photocell, and no variation was noted between this trace and that obtained with the bellows. Thus, the pressure of the probe against the chest wall does not appear to alter significantly the configuration or amplitude of the precordial movements As most of the other types of transducers are somewhat difficult to manipulate and offer no more accuracy (in many cases they are less accurate due to difficulties encountered with electronic amplifiers), the bellows was chosen as the simplest and most reliable means of recording the precordial impulses The bellows is mounted on a cross bar above the patient so that the probe of the bellows can be placed anywhere over the chest wall This is important since there are many abnormalities encountered in precordial motion other than those at the apex The frame can be mounted permanently on any bed or can be made portable Thus, records can be obtained without moving the patient, and even with the patient propped up in bed Traces are obtained from various points over the precordium, usually corresponding to the V leads in the electrocardiogram, and from epigastric areas just below the right costal margin in the right midclavicular line and from the epigastric area just below the ziphoid process These are designated as K_1, K_2, etc., corresponding to the electrocardiographic unipolar chest leads In addition, it is sometimes desirable to take records from multiple points over the entire anterior chest wall. Recordings are taken during sustained normal expiration, as the movements due to breathing cause large swings in the baseline. This has appeared no real handicap, as almost all patients can hold their breaths while the complexes are being recorded.

Physical principles. Very little is known about the relationship between the motion of the heart and of the overlying chest wall; however, certain aspects should be mentioned Any activity of the heart including the motions of the heart, changes in intrathoracic pressure and closure of valves can set the chest wall into vibration. These vibrations represent a spectrum of frequencies ranging from palpable phenomena to those which are audible such as the heart sounds and murmurs The technic under discussion involves the recording of the low end of the scale (approximately between 1 and 20 cps) with the major components lying between 1 and 10 cps (as determined by Fourier analysis) Setting the chest wall into vibration by percussion indicates that the natural frequency of the chest wall is above 75 cps This is sufficiently high so that frequencies between 1 and 20 cps should be accurately transmitted by the precordium without distortion However, it is still not certain whether all vibrations imparted to the chest wall by the heart are accurately transmitted in phase with the basic motion of the heart. It is possible that some distortion in phase and amplitude will occur although thickness and physical characteristics of the chest wall exert very little influence over the contour of the trace recorded It should be mentioned that traces obtained from normal obese patients are similar in pattern to others but reduced in amplitude Accordingly, because of the marked physical differences from one chest wall to another, it has not appeared advisable to establish amplitude criteria

Cadaver studies have shown that the entire chest wall moves as a unit [15] A slight tap within the chest wall in cadavers produces a movement of the ribs as well as the intercostal spaces Also, the motion recorded from such a tap is of maximum amplitude when the probe is directed over the point of tap The amplitude diminishes as the probe is moved away from the impulse The movements do not necessarily represent immediately the underlying point of motion, since point motion beneath the precordium is reflected over a wide area. Thus, no movement is due solely to the activity or motion of a small part of heart just beneath the probe The movements can be considered somewhat analogous to the electrocardiographic V leads Although there is vectoral representation

prominent in the V_1 and V_2 areas in the second intercostal space A possible relationship to the distention of blood in the aorta and pulmonary artery with displacement of the heart forward, has been considered The amplitude and shape of the systolic movements depend at least in part on the relative magnitude of the force produced by the blood entering the great vessels and the degree of retraction of chest wall associated with the ejection One would tend to produce an outward movement while the other favors an inward motion. The net effect probably would be related to the force that occurs dominantly As the retraction of the chest is taking place during mid and late systole (continued volume change), the previous outward movement may continue outward or move inward depending again on balance of these factors.

About the time or just before occurrence of the carotid incisural notch there is usually a small abrupt outward movement of the entire precordium It is assumed that this phenomenon is one of relaxation, as with the inward movement which follows The exact mechanism is uncertain other than a probable relationship to the phenomena of relaxation The subsequent outward movement in early diastole occurs about 08 to 10 second following the incisural notch in the carotid pulse and probably represents ventricular filling, since the onset correlates with the opening snap as in patients with mitral stenosis [39]

The atrial portion, the movements as noted in the electrocardiogram between the onset of the P waves of the QRS complex, often are relatively small, anteriorly and posteriorly However, in patients with enlarged atrial or increased atrial pressure there frequently is an exaggeration of the presystolic movements, and often these continue past the onset of the QRS complex, depending on the PR interval These usually can be separated from motions due to ventricular activity, since there is a very abrupt change in the motion with the onset of ventricular contraction approximately 04 second after the onset of the QRS complex.

Traces from patients with abnormal hearts become understandable if one considers that in general the early systolic outward movement over the precordium is of right ventricular origin. The apex thrust is of left ventricular origin. The precordium in general retracts during systole, and the outward movement during early diastole is a filling phenomenon.

The normal kinetocardiogram In general, all normal traces are similar when compared with records obtained from comparable points over the precordium [33-35] Indeed, the variations are primarily related to a change in the relative amplitudes of various movements. Subjects with marked overactivity of the heart or those in a hyperkinetic state show an exaggeration of all movements The apex impulse may be prominent in some normal subjects, probably due to the proximity of the heart to the chest wall However, in normal subjects there is still a retraction of the apical portion of the chest wall during ejection Other small variations occur, the early systolic outward movement may be manifested only in the V_1 area and absent over the other points of the precordium Retraction of the precordium in the region of the apex, just prior to the onset of the apex thrust, is variable and may be very small in certain normal subjects with prominent apex thrust Although such minor variations in the traces appear as indicated, the general features discussed under "Genesis" are noteworthy in all subjects so far studied

Clinical Use of the Kinetocardiogram

The kinetocardiographic technic in clinical medicine is just beginning to be established Although analysis at the present time is still empiric and based primarily on contour of the kinetocardiographic traces, the findings are sufficiently consistent in certain disease states to be useful In addition, it appears that some quantitation of the kinetocardiogram can be achieved, since preliminary studies have shown that the changes can be partially quantitated with pulmonary artery pressures This will be discussed subsequently.

Right Ventricular Hypertrophy

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right ventricular hypertrophy The graphic

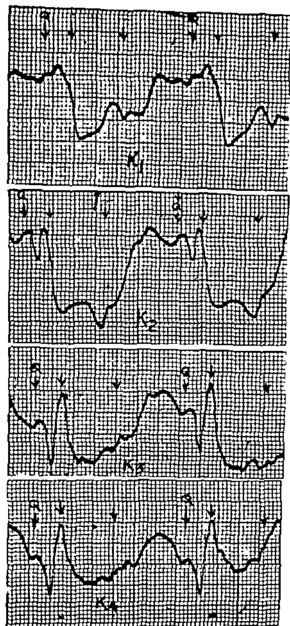


FIG 3—A representative normal kinetocardiogram The arrow labeled *Q* indicates the onset of the QRS complex of the electrocardiogram, the second arrow, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch K_1, K_2, K_3 and K_4 traces are presented which correspond to the precordial unipolar V leads Paper speed is 50 mm per second Note that the segment just preceding the onset of the QRS complex has small low-frequency movements which are presumed to be auricular in origin as they occur after the onset of the P wave in the electrocardiogram and before ventricular excitation There is a small abrupt outward movement approximately 01 second after the QRS complex, followed by a retraction which begins before ejection but continues into the ejection phase Note that in the K_3 and K_4 traces there is a prominent outward movement beginning after the

hypertrophy in whom the early systolic outward movement over the entire precordium is always exaggerated. Approximately 06 second after the onset of the QRS complex there is an inward motion over the left precordium associated with a continued outward movement over the right side of the anterior chest wall (K_1) Since this occurs before ejection, it is assumed to be due to a shape change of the heart, possibly ventricular shortening, The K_1 area usually moves abruptly inward about 08 second It is possible that the inward movement at this point may be an indication of right ventricular ejection. Also approximately 08 second after the onset of the QRS complex there is an outward movement in the region of the apex which represents the true apex thrust The apex thrust is considered to be due primarily to left ventricular activity (possibly to a clockwise rotation of the heart with an anterior lift of the apex) The often markedly exaggerated apex impulse in patients with left ventricular hypertrophy offers the best evidence that it is due to left ventricular activity

The systolic ejection phase portion of the cardiac cycle is characterized by retraction of the entire precordium Since traces from different points over the precordium retract (move inward) during early ejection, it is assumed they are the result of changes in interthoracic volume or pressure associated with blood rapidly leaving the heart and thoracic cavity (A decrease in heart size would also produce a retraction of the precordium) During midsystole there is usually a small outward movement even though the entire chest wall is still *retracted* below the diastolic or resting level This outward movement is most prominent in the V_1 area, however, it may be registered over the entire precordium It occurs during midsystole and correlates fairly well with the J wave in the ballistocardiogram and is most

FIG 3—*Continued*

QRS complex of the electrocardiogram and before ejection which reaches a peak about the time when ejection begins This motion represents the true apical impulse Again, there is a retraction of the precordium during the ejection phase The prominent outward movement after the third arrow or the incisural notch represents the onset of ventricular filling

In patients with interatrial septal defects in whom the shunt was reversed, due to an elevated pulmonary artery pressure, the traces resemble those of mitral stenosis with a prominent midsystolic outward movement (Fig. 6) The differences may be expressed mathematically by dividing the amplitude of the early outward systolic movement by the amplitude of the retraction during ejection This ratio was found to be less than one in patients without significant pulmonary hypertension and with an increased minute flow, and greater than one in patients with pulmonary hypertension The duration of the outward movement as measured from the onset of the outward movement to the point where the trace again crosses the base line also is significant. The duration in patients without pulmonary hypertension did not exceed 24 second, however, in patients with elevations of the pulmonary artery pressure the duration was 30 second or greater Thus, the kinetocardiogram offers a means by which flow loads of the right ventricle can be "differentiated from pressure loads" The early systolic outward movement probably is the result of definite hypertrophy of the right ventricle, while the midsystolic outward movement in some way reflects the pressure load The kinetocardiographic changes following mitral valvulotomy also support the view that midsystolic outward movements are closely related to pressure phenomena, for the curves display a marked diminution of this movement, as early as 10 days after the operation.[27] However, the early systolic outward movement may persist as long as one year and actually never revert in patients with a satisfactory valvulotomy In contrast to the consistent kinetocardiographic findings, the electrocardiograms may be normal

It is uncertain as to whether the kinetocardiographic changes as described are the result of true anatomic hypertrophy of the right ventricle or the indication of an unduly forceful right ventricle. Correlation of the weight of

tion Thus, regardless of etiology and the anatomic developments of the heart kinetocar-

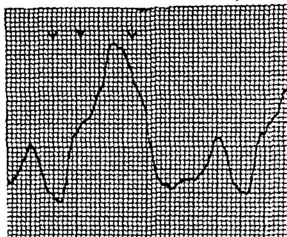


Fig 6—A K_1 trace from a patient with interatrial septal defect with pulmonary hypertension and reversal of the interatrial shunt flow First arrow indicates onset of the QRS complex of the electrocardiogram; the second arrow, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch The paper speed was 50 mm per second Note that the trace resembles that of mitral stenosis with a marked pre-ejection outward movement and a marked mid-systolic outward movement as well.

diography is a valuable tool for differentiating right ventricular pressure loads from flow loads

Recent studies indicate that it may be possible to estimate pulmonary arterial pressure as well as total pulmonary vascular resistance from the kinetocardiogram.[33] The ratio obtained by dividing the amplitude of the right ventricular measurement by the amplitude of the systolic retraction (K_1 trace) has a significant correlation with these physiologic measurements The scatter is large and there are exceptions (notably pulmonic stenosis) However, the ratio is useful in following patients for changes in pulmonary artery pressure and pulmonary vascular resistance.

The most significant feature of the kinetrocardiogram in left ventricular hypertrophy is a well localized, exaggerated apical impulse.[30] In addition, there are certain differences in the apical impulse, depending on the etiology Hypertension, aortic stenosis and occasionally mitral insufficiency (left ventricular pressure loads) are primarily characterized by a conspicuous exaggeration of the apical impulse which begins .04 to .08 second after the onset

representation of these movements by the kinetocardiogram has offered some evidence of its reliability A recent study comparing patients with right ventricular hypertrophy due to increased pulmonary vascular resistance and patients with increased flow loads in the right ventricle without elevated pulmonary artery pressures (interatrial septal defects) has shown differences between the two groups [12] FIGURE 4 illustrates a typical trace in a patient with mitral stenosis in whom the pulmonary artery pressure was elevated The trace is characterized by a marked outward movement of the precordium extended throughout the period of systole, beginning soon after the onset of ventricular systole (.04 to .06 second after the onset of the QRS complex of the electrocardiogram) At the onset of ejection there is a brief inward movement followed by a second outward *movement, reaching a peak in midsystole.* These outward movements of the precordium are usually most prominent at the K_2 point, but the distribution is often from K_1 through K_4. In patients in whom the pulmonary artery pressure was markedly elevated (over 50 mm. Hg) the outward movements were most prominent over the right precordial area (K_1), rather than to the left of the sternum. In contrast, patients with an interatrial septal defect with a marked increase in right ventricular flow load but without pulmonary hypertension are similarly characterized by prominent early systolic outward movement, however, at the onset of ejection there is marked retraction and an absence of the mid-systolic outward movement (FIG. 5)

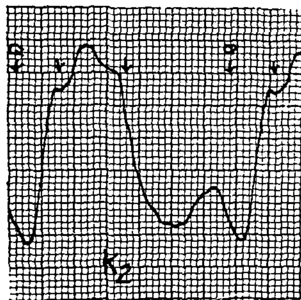


FIG 4.—A trace taken from the K_2 position from a patient with *mitral stenosis and pulmonary hypertension* The onset of the QRS complex of the electrocardiogram is indicated by the first arrow labeled *Q* The second arrow indicates the onset of ejection as determined by the upstroke in the carotid pulse The third arrow *indicates the end of ejection as determined* by the carotid incisural notch Trace was taken at a paper speed of 50 mm per second Note the prominent early systolic outward movement of the anterior precordium which reaches a peak about the time of the *onset of ejection* At the onset of ejection there is a very brief retraction followed by an outward movement in midsystole This midsystolic outward movement is prominent in patients with mitral stenosis with pulmonary hypertension The duration of the total outward amplitude is significantly prolonged both over normal subjects as well as patients with interatrial septal defects

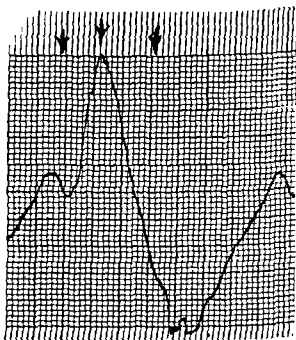


FIG 5.—A trace taken from the K_2 position in a patient with interatrial septal defect without significant pulmonary hypertension First arrow indicates onset of the QRS complex of the electrocardiogram; the second, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch Note the prominent preejection outward movement in the trace, followed by an abrupt inward movement during ejection The total duration of the outward movement is *significantly* prolonged over that of normal subjects

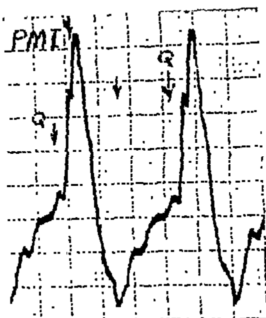


FIG 9.—A K_5 trace (PMI) from a patient with severe aortic insufficiency The paper speed is only 25 mm per second First arrow marked Q represents onset of the QRS complex, the second arrow, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch Note that the apical impulse in aortic insufficiency is characterized by a very marked outward movement of the apex, beginning about 01 second after the onset of the QRS complex The outward movement reaches a peak about the time of ejection but retracts during the major part of ejection This is in contrast to patients with left ventricular hypertrophy due to pressure loads where there is a sustained outward movement during ejection

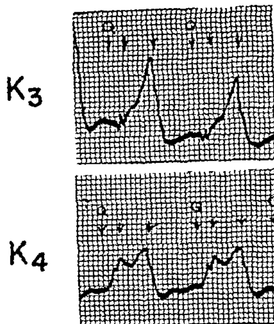


FIG 10.—A trace taken from a patient with pure mitral insufficiency A paper speed of 25 mm per second was used The first arrow indicates onset of the QRS complex of the electrocardiogram, the second arrow, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch Note that the K_3 and K_4 traces show a marked late systolic outward movement which reaches a peak just before the end of ejection as indicated by the carotid incisural notch This feature has been found to be present in most instances of patients with significant mitral insufficiency

volved Thus, patients with mitral stenosis and pulmonary hypertension reveal the typical pattern of right ventricular hypertrophy with an early and midsystolic outward movement of the precordium, as illustrated in FIGURE 4 [36] Patients with mitral insufficiency usually reveal a somewhat different type of trace (FIG 10),[42] characterized by a prominent late systolic outward movement of the precordium, reaching a peak close to the end of ejection as determined by the carotid incisural notch This is usually a generalized precordial phenomenon, however, it may be more striking in the region of the apex of the K_3 area While this type of record is found in the majority of the patients with mitral insufficiency, a few patients have been encountered with a prominent apical impulse only, as noted in patients with left ventricular hypertrophy due to other causes

Although the kinetocardiogram primarily reflects the degree of hypertrophy of the respective ventricles, it does offer some differentiation of the valvular lesions Predominant mitral insufficiency in the presence of minimal mitral stenosis usually has a trace with a prominent late systolic outward movement In addition, an isolated large apical impulse along with a prominent right ventricular movement is strong evidence of functional, significant mitral insufficiency No instance has been encountered so far where a predominant mitral insufficiency was present when the trace revealed only the right ventricular type pattern. In addition, the absence of a right ventricular type pattern is strong evidence against a significant functional mitral stenosis

Aortic valvular lesions produce the changes

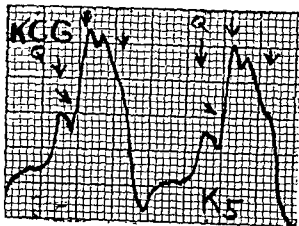


FIG 7—A trace of the point of maximum impulse (K_5) from a patient with left ventricular hypertrophy due to hypertension The first arrow indicates the onset of the QRS complex of the electrocardiogram, the second arrow, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch The paper speed was 25 mm per second The diagonal arrow indicates the outward movement of the "true" apex thrust Note that the thrust begins approximately 08 seconds after the onset of the QRS complex and reaches a peak about the time of ejection In contrast to patients with aortic insufficiency, there is a more sustained outward movement throughout the entire phase of ejection, rather than a marked retraction

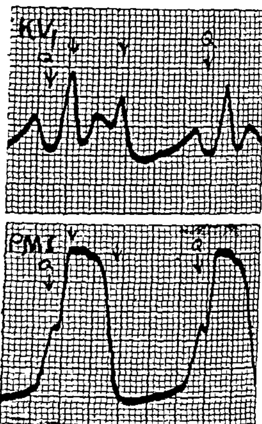


FIG 8—Representation of the K_1 and K_5 traces from a patient with both left and right ventricular hypertrophy The first arrow indicates the onset of the QRS complex, the second arrow, the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow, the onset of the carotid incisural notch The paper speed was 25 mm per second Notice that in the PMI trace (K_5) there is a prominent outward systolic movement which is greatly exaggerated The first portion of the outward movement begins before the onset of the QRS complex and is presumed to be auricular in origin In addition to the exaggerated apical impulse of left ventricular hypertrophy, the K_1 trace (*above*) demonstrates a prominent outward movement shortly after the onset of the QRS complex similar to that noted in patients with right ventricular hypertrophy Thus, patients with both left and right ventricular hypertrophy may have kinetocardiographic features common to both disorders

of the QRS complex of the electrocardiogram (FIG 7). The prominent outward movement is usually well sustained throughout systole and retracts only during the terminal portion of systole and early part of diastole This is usually associated with relatively normal traces over the rest of the precordium, unless right ventricular hypertrophy is also present In this instance, there is the outward precordial heave in addition to the marked exaggeration of the apical impulse (FIG 8) Patients with aortic insufficiency display a somewhat different apical impulse (FIG. 9) The early systolic pre-ejection portion or outward movement of the impulse resembles other types of left ventricular hypertrophy; however, with the onset of ejection there is usually a distinct retraction (inward movement) giving a very exaggerated peak but brief outward movement [28] The nonsustained impulse is probably due to the rapid runoff of blood and large stroke volumes from the left ventricle in aortic insufficiency This results in retraction of the impulse during ejection. Certain patients with mitral insufficiency present an entirely different type of apical impulse, as mentioned in the considerations of valvular heart disease

Valvular Heart Disease

The kinetocardiographic changes as a result of valvular heart disease are primarily due to hypertrophy or a predominantly functioning ventricle, depending on the heart valve in-

Bulges occasionally are confused with traces noted in other types of heart disease With extensive infarction, the entire precordium may be displaced outward during systole and resemble the pattern noted in right ventricular hypertrophy. Thus, only historical evidence will provide critical information to differentiate the two conditions In addition, if the infarction occurs at the apex the paradoxic motion will be localized at this point and resemble the apical impulse of left ventricular hypertrophy.

Angina pectoris Some patients with angina pectoris may display a paradoxic motion at some point over the precordium during systole, even at rest; and with exercise approximately 75 per cent of the patients will show an aneurysmal bulge[37] Other patients without precordial bulges may show abnormal tracings and with some, there may be a normal kinetocardiogram The mechanism of a persistent bulge in a patient with angina pectoris at rest is not entirely clear It is possible that this represents an old myocardial infarction or a chronic ischemic area of noncontracted ventricular muscle. As for the latter, there is evidence that such bulges tend to disappear after the administration of nitroglycerine.

Conduction defects. Studies have been concerned with the presence or absence of aneurysmal bulges in patients with electrocardiographic evidence of either left or right bundle-branch block and interventricular conduction defects[29] Approximately 70 per cent of the patients with left bundle-branch block had a paradoxic aneurysm recorded from some point over the precordium However, only 50 per cent of the patients with right bundle-branch block had demonstrable "bulges" It is interesting that some patients presented no evidence of any form of heart disease other than the electrocardiographic abnormality, and in general no bulge could be demonstrated. However, bulges were noted in approximately 60 per cent of the patients who had interventricular conduction defects.

Variations in the kinetocardiograms have been noted in other types of heart disease, but the data have not been sufficiently evaluated for discussion in the present chapter.

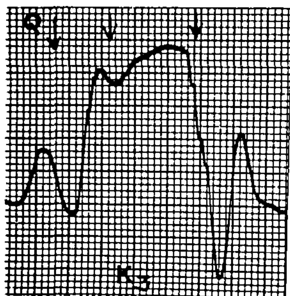
Electrokymography

Electrokymograms are the graphically recorded movements of the various borders of the heart The technic was first introduced in 1947 by Henny and Boone and initially aroused considerable interest in the United States,[48] but in recent years the use of the electrokymograph has markedly diminished. However, in some of the Scandinavian, European and Latin American countries the interest has continued with active investigation.

Methods The apparatus consists of a photocell with a small linear slit which is placed transversely across the heart border for fluoroscopic observation As the heart moves back and forth, the intensity of the x-ray beam will change, and thus the amount of light thrown on a fluorescent screen in front of a photocell will vary. This results in a changing electrical output which is amplified and recorded. In addition, if the photocell is placed over the mass of the heart a densogram also can be recorded.

The circuits of the amplifiers currently used have inherent limitations for several reasons. Even the beam of a full-wave fluoroscope is somewhat pulsatile, and as a result the very sensitive photocells change their output. To eliminate these fluctuations, a complex network of filters is necessary which inadvertently alters the frequency characteristics of the instrument and results in some shift of phase as well as a lag in the recorded signal. In addition, linearity of the apparatus is a problem The photocell does not possess the same electrical output from every point over the photosensitive surface Thus the photocell itself is nonlinear Although the traces are reasonably accurate, they contain only low-frequency movements and lack the precision and quantitation desired. These objections have been overcome to some extent by specially designed apparatuses such as the quantitative electrokymograph introduced by Morgan.[50] However, it has never been commercially available.

The equipment manufactured in Scandinavia in general has much better characteristics than the amplifiers made in the United States in that the frequency range has been extended above that noted in the models obtained in this country. In general, the commercial



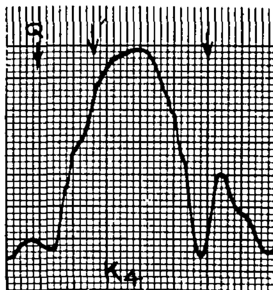


FIG 11 —K_3 and K_4 traces from a patient with an anterior myocardial infarction First arrow indicates onset of the QRS complex of the electrocardiogram, the second arrow, the upstroke in the carotid pulse, and the third arrow, the carotid incisural notch The paper speed was 50 mm per second Approximately 04 second after the onset of electrical activation of the heart, there is a prominent outward movement (bulge) in the K_3 and K_4 positions which is sustained throughout most of ejection The bulge when due to an anterior myocardial infarction is usually more prominent at the K_4 position Posterior myocardial infarctions are more apt to have a bulge in the epigastric areas

in the apical impulse as described under hypertrophy. Although the apical impulses in aortic stenosis and aortic insufficiency are different, as mentioned, these have been quantitated and correlated with the actual degree of regurgitation or stenosis to offer reliability in estimating the degree of aortic insufficiency in a patient with combined aortic lesions

Coronary Artery Disease

Myocardial infarction. Myocardial infarction results in a systolic paradoxic (outward) movement of the precordium generally over the area of the infarct in contrast to the retraction which occurs during ejection in normal subjects (FIG. 11) In a recent study of acute myocardial infarctions these have been present in 100 per cent of the patients whether the infarct was posterior or anterior.[91] The most prominent "bulge" in patients with posterior infarctions was more frequent in the epigastric areas, while the bulge in patients with anterior infarctions was of maximum amplitude at the K_3 area The bulge in approximately 78 per cent of the hospitalized patients persisted for a period of four weeks, of which 22 per cent returned to normal during follow-up observation Thus the majority of patients with myocardial infarction (regardless of the age of the infarct) will reveal a persistent aneurysmal bulge recorded by the kinetocardiograph These alterations may or may not be due to true anatomic myocardial aneurysms Some are certainly functional systolic bulgings of the myocardium similar to the findings in dogs when one of the branches of the coronary artery is ligated Many of the paradoxic movements in patients can be felt at the bedside; the rest are only recorded on the kinetocardiographic trace It is surprising that posterior infarctions often had paradoxic motions over the anterior precordium as well as in the epigastric area It is presumed that these were due to an infarction of the interventricular septum with bulging of the septum into the right ventricle, producing the outward movement over the anterior precordium Although the kinetocardiogram obviously does not indicate the age of the infarct, it may be of definite value in differentiating status anginosis or coronary insufficiency from myocardial infarction Indeed, a bulge which persists after the cessation of pain is strong evidence that a myocardial infarction is present

Bulges occasionally are confused with traces noted in other types of heart disease. With extensive infarction, the entire precordium may be displaced outward during systole and resemble the pattern noted in right ventricular hypertrophy Thus, only historical evidence will provide critical information to differentiate the two conditions In addition, if the infarction occurs at the apex the paradoxic motion will be localized at this point and resemble the apical impulse of left ventricular hypertrophy

Angina pectoris. Some patients with angina pectoris may display a paradoxic motion at some point over the precordium during systole, even at rest; and with exercise approximately 75 per cent of the patients will show an aneurysmal bulge.[37] Other patients without precordial bulges may show abnormal tracings and with some, there may be a normal kinetocardiogram. The mechanism of a persistent bulge in a patient with angina pectoris at rest is not entirely clear. It is possible that this represents an old myocardial infarction or a chronic ischemic area of noncontracted ventricular muscle As for the latter, there is evidence that such bulges tend to disappear after the administration of nitroglycerine

Conduction defects Studies have been concerned with the presence or absence of aneurysmal bulges in patients with electrocardiographic evidence of either left or right bundle-branch block and interventricular conduction defects[28] Approximately 70 per cent of the patients with left bundle-branch block had a paradoxic aneurysm recorded from some point over the precordium. However, only 50 per cent of the patients with right bundle-branch block had demonstrable "bulges." It is interesting that some patients presented no evidence of any form of heart disease other than the electrocardiographic abnormality, and in general no bulge could be demonstrated However, bulges were noted in approximately 60 per cent of the patients who had interventricular conduction defects

Variations in the kinetocardiograms have been noted in other types of heart disease, but the data have not been sufficiently evaluated for discussion in the present chapter

Electrokymography

Electrokymograms are the graphically recorded movements of the various borders of the heart. The technic was first introduced in 1947 by Henny and Boone and initially aroused considerable interest in the United States,[49] but in recent years the use of the electrokymograph has markedly diminished. However, in some of the Scandinavian, European and Latin American countries the interest has continued with active investigation

Methods. The apparatus consists of a photocell with a small linear slit which is placed transversely across the heart border for fluoroscopic observation. As the heart moves back and forth, the intensity of the x-ray beam will change, and thus the amount of light thrown on a fluorescent screen in front of a photocell will vary This results in a changing electrical output which is amplified and recorded In addition, if the photocell is placed over the mass of the heart a densogram also can be recorded.

The circuits of the amplifiers currently used have inherent limitations for several reasons Even the beam of a full-wave fluoroscope is somewhat pulsatile, and as a result the very sensitive photocells change their output. To eliminate these fluctuations, a complex network of filters is necessary which inadvertently alters the frequency characteristics of the instrument and results in some shift of phase as well as a lag in the recorded signal In addition, linearity of the apparatus is a problem The photocell does not possess the same electrical output from every point over the photosensitive surface Thus the photocell itself is nonlinear Although the traces are reasonably accurate, they contain only low-frequency movements and lack the precision and quantitation desired These objections have been overcome to some extent by specially designed apparatuses such as the quantitative electrokymograph introduced by Morgan[50] However, it has never been commercially available

The equipment manufactured in Scandinavia in general has much better characteristics than the amplifiers made in the United States in that the frequency range has been extended above that noted in the models obtained in this country In general, the commercial

United States electrokymographs show a significant attenuation of the signal about 8 to 10 cps and have very little or no response to signals in the range of 20 cps, in contrast to the Swedish instruments which are fairly linear up to 20 cps

Interpretation of the electrokymogram It has been generally assumed that the electrokymograms are essentially modified ventricular volume curves To obtain more exact knowledge studies of the cardiac cycle have been undertaken in human subjects It appears that the onset of ventricular filling is delineated, but the onset of ejection is poorly defined, and traces from the ascending aorta have become necessary in order to separate the systolic phases of the cardiac cycle The assumption that the traces are volume curves is apparently oversimplified in light of the many positional changes and alterations in the great vessels and cardiac silhouette Thus, the major problem in understanding and interpreting electrokymographic traces has been the difficulty in separating or ascertaining the parts that represent volume, position and contour of the heart Positioning of the photocell also causes difficulties, although the examiner is able to see where the slit of the photocell is placed The problem actually concerns the identification of the heart chamber that produces the trace It is often apparent from traces that a mixture of movements has developed from two heart chambers even though from observation the photocell is apparently located over a definite part of the heart This uncertainty adds to the difficulties of interpretation. These problems have contributed to the decreasing popularity of the electrokymograph

Clinical use of the electrokymograms The electrokymographic technic has been applied to the study of many forms of heart disease and the reader is referred to a recent monograph by Dussailant [46] In general the clinical studies have not contributed much useful information Only a few examples will be mentioned. The reports in detecting mitral insufficiency are *conflicting* [43, 49, 50, 52] *A large* pansystolic outward movement of the left auricle is apparently characteristic of mitral insufficiency.[47, 49] However, the patients in which this is present usually offer no difficulty in recognizing the lesion at the bedside Myocardial aneurysms have been studied with the electrokymographic technic and paradoxic pulsations of the ventricles are frequently present over the area of the myocardial infarction [44] Congenital heart lesions apparently produce some significant electrokymographic changes [48] However, more direct technics such as cardiac catheterization and angiocardiography are necessary (in view of the current widespread use of open heart surgery) for a precise demonstration of the anatomic defect It appears that electrokymographic studies for clinical purposes are not justified at the present time due to radiation exposure, and the limited amount of information obtained by this technic It still remains a research technic

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Measurement of Coronary Blood Flow and Myocardial Metabolism

By GEORGE G. ROWE, M.D.

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IT has been estimated that of the total deaths due to heart disease one-third may be attributed to primary coronary artery insufficiency related to atherosclerosis as the dominant factor, one-third to primary coronary insufficiency associated with cardiac hypertrophy and increased work arising from valvular lesions and increased blood pressure and one-third to primary myocardial insufficiency In other words, two-thirds of the deaths from heart disease may be traced directly or indirectly to coronary artery insufficiency If this is true, it is of prime importance, whenever heart disease is presented, to consider the blood supply of the myocardium Only in relatively recent years has the study of coronary blood flow of intact animals and man become possible; yet sufficient information has already accumulated for critical evaluation Such an evaluation should rest on a brief review of the known anatomic facts concerning the coronary circulation.

Comparative anatomic considerations of the coronary circulation reveal that in more primitive forms, such as the lamprey, the myocardium is spongy and trabecular in character and receives its nutrition by diffusion from the blood passing within its chambers and through the intertrabecular spaces. In more highly developed forms and particularly as the myocardial wall becomes thicker, the cortical layer of myocardium becomes so compact that a separate vascular system is developed. These new vessels to the myocardium come phylogenetically and embryologically from the proximal ends of the major inflow and outflow vessels of the heart tube as well as through the cardiac ligaments of lower forms

The accessory sources of blood supply along the pericardial reflections are lost to adult man except as collateral circulation and reach clinical significance only when artificially or pathologically augmented. During the course of development of the lower mammalian and human heart, the coronary vascular system comes late, and in the early stages the myocardium is nourished by the blood within its cavities. Perhaps as a remnant of this primitive form of nutrition to the myocardium are found the musculae pectinatae of the atria, the columnae carneae of the ventricles and the extensive connections of the adult coronary vascular system to the lumina of the ventricular chambers Thus, Wearn described arterioluminal vessels running from the coronary arteries through the myocardium to the ventricular cavities, arterioluminal sinusoids passing deviously through the myocardium, connecting the arterial lumen to the ventricular cavity and the Thebesian veins communicating with the coronary venous system and the ventricular lumen. When one considers these in addition to the capillary network, some resemblance to the original phylogenetic and ontogenetic myocardial "sponge" is maintained. This extensive system of vessels within the myocardium, as well as the anastomoses through the pericardial reflections to mediastinal vessels, is the apparent reason why survival is possible after complete occlusion of both coronary arteries.

Gross anatomic consideration of the distribution of the coronary vessels reveals that of 359 human hearts whose description was summarized by Adachi in 1923, 67.7 per cent had an essentially balanced coronary artery system in which the right and left coronary arteries supplied roughly equal portions of the myocardium In 21.6 per cent, the right coronary artery was predominant in that it encircled the heart further than usual and sup-

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and much valuable information has been derived from their employment[18] The former has furnished information concerning phasic flow, since, depending on the pressure gradient across an orifice, it is sensitive to rapid changes both in volume and direction of flow; the latter which measures *flow by its ability to elevate* a suspended body in a vertical tube has been most valuable where determination of mean flow is desired

A bubble flow meter has been used in pharmacologic and physiologic investigations[14] of coronary flow and the electromagnetic flow meter has its advocates The nitrous oxide (N_2O) method, because of its ready application to the intact anesthetized animal and to the unanesthetized human, has been widely used for determining coronary flow, and most of the information derived from human subjects has been gained through its use. A method has been proposed in which coronary blood flow may be determined by radioactive rubidium since it is taken up by the myocardium and the curve of its uptake may be obtained from the precordial surface by quantitation of the increase in radioactivity. Further validation of the method is required before widespread acceptance, particularly since the fraction of rubidium taken up by the heart may vary from time to time

An intriguing visual method of demonstration of the coronary circulation is that in which the coronary arteries of the intact dog are cannulated, injected with contrast substance and radiographs taken to demonstrate the pattern of the coronary vessels before and after administration of various pharmacologic agents. This method has been employed exclusively in experimental animals; also visualization of coronary arteries by injection of contrast substances into the root of the aorta or into the coronary vessels themselves has been done clinically to evaluate patients with angina pectoris

The extensive use of the N_2O method for determination of coronary blood flow in man justifies further discussion of the technic of its application. The method basically is adapted from the cerebral flow technic of Kety and Schmidt and depends on the fact that the myocardium takes up N_2O rapidly from the blood which perfuses it. If the quantity of N_2O which has been taken up by the myocardium in a given period is known and if the arteriovenous difference of N_2O across the myocardium is known, calculation of blood flow per 100 Gm of myocardium per minute may be done by the Fick principle. The basic technic requires simultaneous sampling of blood from a peripheral artery and the coronary sinus so that arterial and venous specimens on each side of the myocardium can be obtained. Fifteen per cent N_2O in a gas mixture containing 65 per cent nitrogen and 21 per cent oxygen is then administered throughout a 10 minute period and multiple blood samples are drawn from the arterial and venous side of the myocardial circulation On the assumption that equilibrium is reached in this 10 minute period, the final venous level represents the final myocardial level of N_2O Since the arteriovenous difference can be calculated from the multiple points on the arterial and venous N_2O curves, the Fick principle can be applied and coronary flow calculated in milliliters of blood flow per 100 Gm of left ventricular myocardium per minute Certain basic problems are involved in the N_2O method of determining coronary blood flow, not the least of which is the procedure of cardiac catheterization where a certain amount of apprehension on the part of the subject is natural. In addition, placement of the catheter in the coronary sinus may be difficult due to the anatomic characteristics of the thebesian and eustachian valves Hellerstein and Orbison have concluded that these valves are of such disposition and character that catheterization of the coronary sinus is possible in only 75 per cent of cases Clinical experience indicates that in at least 75 per cent of patients the coronary sinus can be catheterized and generally 80 to 90 per cent of attempts should be successful depending somewhat on the selection of cases. There is a further disadvantage since the method requires a 10 minute "steady state" to determine a single coronary flow An even greater disadvantage is the fact that it is not possible to measure flow continuously Complications of the method in our experience with

plied not only most of the right ventricle and posterior interventricular groove but also part of the posterior wall of the left ventricle beyond the ventricular groove In 10 7 per cent of these hearts the left coronary artery was predominant, supplying not only the left ventricle but also the posterior surface of the heart including the interventricular groove and portions of the posterior wall of the right ventricle

Further gross variations of the coronary arteries may be considered under the general heading of their point of division into branches, since they may divide early or late in their course from the aorta to the myocardium. The most common pattern is that of the coronary vessels arising independently as right and left coronary arteries, disseminating their usual branches to the myocardium The second or intermediate variation to be considered is that in which not only the right and left coronary arteries arise from the aorta but also accessory orifices into the aorta, whence arise the circumflex or other vessels which are normally branches of the right and left coronary artery proper Perhaps the least common variation is that of both coronary arteries arising from the aorta by a common trunk These may assume either the usual course of the right or left coronary artery, divide into two branches which are recognizable in course and distribution as the right and left coronary artery or form arborizations which *are not compatible with the usual description* of either or both of the coronary arteries Uncommon, but clinically important variants of the coronary vessels consist of an anomalous connection of coronary arteries in which they may rise from the pulmonary artery or in which abnormal communications exist between the coronary arteries and the cardiac chambers or the cardiac venous system.

The cardiac venous system consists primarily of the left ventricular venous network ending in the coronary sinus and the right ventricular venous system ending in the anterior cardiac veins which drain into the right atrium. A small portion of the right ventricle normally drains into the coronary sinus.

It is apparent in such a *complex anatomic* system as the coronary vasculature, that exact measurements of flow are impossible, and that the numerous methods used for determining the coronary blood flow are an index of the inherent difficulty involved in this study. In general, the most accurate methods require surgical procedures with more or less complete exposure of the heart and hence raise some question as to the validity of comparing results obtained with the normal intact animal On the other hand, methods that can be used in the intact preparation do not present the same degree of accuracy, controllability and continuity which can be obtained in the more isolated and hence somewhat more artificial heart preparation Furthermore, those procedures which require anesthesia demand independent evaluation of the effects of the anesthetic agents

Langendorff's method, in which fluid is supplied through the ascending aorta, perfuses the coronary bed and is collected as it runs out of the right atrium, is a time-honored method of investigating the effects of various parameters on coronary vessels Although it is a relatively simple and direct method and has been widely used pharmacologically, it presents all the disadvantages of the isolated specimen The Morawitz cannula, *inserted* through the right atrium into the coronary sinus, has been used to collect coronary sinus blood in both open and closed chest preparations and thus to approximate coronary flow *The method presents the advantage of* being both direct and continuous but with the disadvantage one must assume, i e , that a constant fraction of the coronary circulation is being measured and that pressure relationships have not been disturbed sufficiently to alter either coronary flow or the fraction of that flow which drains through the cannula.

In furthering the studies of coronary flow thermostromuhr may be placed around the coronary artery. This requires, however, a surgical procedure for placement and there are fundamental problems in its calibration with failure to distinguish forward and backward flow, as well as thermal exchange unrelated to flow Both the orifice meter and rotameter have been used *extensively* in investigations

established partition coefficient in the dog as close enough for the human. Any observer, knowing that a partition coefficient of 1.0 has been used, can easily correct for it by adding 10 per cent to the coronary flow (and to all data referring to the coronary flow in the calculations) if he desires to use the coefficient of 1.1. Another reason for the difference in values from one laboratory to another is that some workers may reject flows in which the arterial and venous N_2O contents do not reach the same concentration at the end of the period of 10 minutes. If this is done, the slower flows in which equilibrium has not been reached at the end of 10 minutes will be excluded and the average flow of the group reported by the investigators will be higher

In referring to TABLE 2, it appears remarkable how similar the coronary blood flow and oxygen consumption per unit weight of heart are in man and in the dog Calculation of efficiency in man is unsatisfactory, because it demands accurate knowledge of the left ventricular weight and at the present time there is no satisfactory way of establishing this in living man If the heart weight is assumed to be a given per cent of total body weight in accordance with Smith's tables for predicting heart weight, figures for myocardial efficiency may be slightly above those of the dog as reported by Gregg[19] Various studies have indicated that the human heart metabolizes glucose, lactate and pyruvate and fatty acids. Considerable variability has been noted in the relation of these substances to metabolism, but the reason for such variability has not been apparent Nevertheless, it is concluded that under basal postabsorptive conditions about 35 per cent of the energy of the heart comes from the utilization of carbohydrates, 6 per cent from amino acids, 4 per cent from ketones, and the remainder from fatty acids.[5] In dogs, relative figures for the consumption of various foodstuffs are as follows. lactate, 34 per cent, glucose, 27 per cent, pyruvate, 5 per cent. But the extraction of these substances was related to the arterial level with the heart metabolizing the substrates most readily available In starving animals, the cardiac R Q falls to 0.70, indicating that fats are utilized almost exclusively. It has been reported[37] that a sex difference in coronary flow exists, with coronary flow per unit weight of the left ventricle being approximately 25 per cent greater in women than in men, associated with increased oxygen consumption of left ventricular muscle of the female heart and accompanied by decreased efficiency (see TABLE 2) Support for this observation is found in the fact that (1) testosterone may decrease oxygen consumption of tissue slices from several organs of rats; (2) the coronary arteries of male babies have a thicker intima and smaller lumen than those of female babies; (3) the ratio of coronary artery circumference to heart weight may be greater in the adult human female than the male[33]; (4) in humans under 40 years of age there is a decidedly greater incidence of coronary artery occlusion in the male than the female and (5) smaller dogs are reported to have a higher coronary blood flow and oxygen consumption per unit weight of heart than larger dogs, apparently as a result of the difference in heart weight The female human heart, being smaller, may have greater flow with an increased oxygen consumption per unit weight.

There has been considerable speculation for many years as to the controlling mechanism for coronary flow[18] Some investigators have believed that the blood vessels are essentially passive, with flow depending on the perfusing pressure and the varying resistance to flow through the coronary circuit, depending on the state of contraction of the myocardium. Certainly, it has been adequately demonstrated that with constant aortic pressure, coronary flow consistently increases during asystole Others have felt that the coronary vessels themselves are active in control of flow through their lumina, their size varying in relation to nervous control or to more direct humoral stimulation from variation in the quantity of oxygen utilized or metabolites produced in the heart muscle Although considerable evidence has been marshalled in support of one or another of these concepts to the exclusion of others, it would appear more reasonable to postulate that mechanical, nervous, humoral and perhaps hormonal influences interact in this control

Since 1883, when Yeo demonstrat[illegible]

over 100 determinations of flow in man have been minimal, consisting of supraventricular tachycardia at times and relatively frequent but minimal thrombophlebitis in the vein through which the catheterization was done Perforation of the coronary sinus has been reported, but occurred under the erroneous assumption that the catheter was located in the right ventricle and that it could be advanced into the pulmonary artery. Whereas in the original method coronary flow was determined during the saturation phase as N_2O was being inhaled and taken up by the heart, some have preferred to use the desaturation phase as N_2O diffuses out of the myocardium Both methods have given the same result The N_2O method checks satisfactorily with the bubble flow meter and the rotameter (±12 per cent) during a steady state

Normal values for coronary blood flow as established with the rotameter, the orifice meter and the nitrous method are summarized for the dog from Gregg[19] in TABLE 1. The data emphasize the relatively high flow of blood per unit weight of heart per minute and the well known fact that the extraction of oxygen from blood perfusing the myocardium is very great with the result that the oxygen content of coronary sinus blood is very low.

TABLE 1—*Normal Values for Coronary Blood Flow in the Dog*

Coronary flow/min /100 Gm of left ventricle = 70–90 ml
Oxygen extraction/100 cc of left coronary blood = 10–15 ml.
Work of left ventricle (CO × BP) = 3–5 Kg -M /min
$\text{Efficiency} = \dfrac{\text{Work of left ventricle}}{\text{Energy equivalent of oxygen used by left ventricle}} \times 100 =$ 15–20%

In general, as indicated in TABLE 2, figures very similar to those given by Gregg for the dog have been obtained in the human although there have been some discrepancies from laboratory to laboratory The differences in findings between laboratories are due in part to the utilization of a different partition coefficient for N_2O across the myocardium.[36] Originally, it was established in the dog that the ratio of N_2O dissolved in myocardium to that dissolved in blood exposed to the same concentration of N_2O was 1 05, under the same conditions with human myocardium and blood, the ratio was 1 13 When the N_2O rate of flow was checked against a bubble flow meter, however, a partition coefficient of 1 0 seemed most adequate and was consequently accepted and used Similarly the ratio of N_2O in blood and in brain or kidney perfused by that blood have been shown to be 1 0 As seen in TABLE 2, some have used the ratio or partition coefficient for human heart to blood of 1 1/1 0 accepting that the human myocardium dissolves slightly more N_2O than blood, but others have not, assuming the empirically

TABLE 2—*Normal Values in the Human*

Parameter	Bing '51[4]	Goodale '53[16]	Calazel '54[9]	Kobayashi '56[22]	Leight '56[24]	Rowe '58[37]	Rowe '58[37]	Ave of to total series (Val of observed × No Cases observed / Total no cases observed)
No of cases	18	5	8	15	8	15	15	84
Age (ave)	—	—	36 54	—	36 4	26	30	30 9
Sex	—	—	6♂ 2♀	—	—	♀	♂	—
Partition coeff	1	1 1	1	—	1 1	1	1	1(1 1)
CBF	77	96(86)*	78	69	103(93)*	98	72	80 6(88 7)
ΔA-CSo_2	12	—	12 2	10 5	10 3	10 9	12 3	11 4
CSo_2	—	—	4 9	—		5 2	6 1	5 5
$CMRo_2$	9 4	—	9 2	7 1	10 5(9 5)*	10 7	8 6	9 0(9 9)

* Corrected to partition coefficient of 1 0 for comparison with other data

CBF = Coronary blood flow in *ml /100 Gm of left ventricle/minute*

ΔA-CSo_2 = Arterial-coronary sinus blood oxygen difference in ml /100 ml of blood

CSo_2 = Coronary sinus blood oxygen content in ml /100 ml of blood

$CMRo_2$ = Cardiac metabolic rate for oxygen—Left ventricular oxygen consumption in ml /100 gm of myocardium/minute

established partition coefficient in the dog as close enough for the human Any observer, knowing that a partition coefficient of 1 0 has been used, can easily correct for it by adding 10 per cent to the coronary flow (and to all data referring to the coronary flow in the calculations) if he desires to use the coefficient of 1.1. Another reason for the difference in values from one laboratory to another is that some workers may reject flows in which the arterial and venous N_2O contents do not reach the same concentration at the end of the period of 10 minutes If this is done, the slower flows in which equilibrium has not been reached at the end of 10 minutes will be excluded and the average flow of the group reported by the investigators will be higher.

In referring to TABLE 2, it appears remarkable how similar the coronary blood flow and oxygen consumption per unit weight of heart are in man and in the dog. Calculation of efficiency in man is unsatisfactory, because it demands accurate knowledge of the left ventricular weight and at the present time there is no satisfactory way of establishing this in living man If the heart weight is assumed to be a given per cent of total body weight in accordance with Smith's tables for predicting heart weight, figures for myocardial efficiency may be slightly above those of the dog as reported by Gregg[19] Various studies have indicated that the human heart metabolizes glucose, lactate and pyruvate and fatty acids Considerable variability has been noted in the relation of these substances to metabolism, but the reason for such variability has not been apparent Nevertheless, it is concluded that under basal postabsorptive conditions about 35 per cent of the energy of the heart comes from the utilization of carbohydrates, 6 per cent from amino acids, 4 per cent from ketones, and the remainder from fatty acids[5] In dogs, relative figures for the consumption of various foodstuffs are as follows. lactate, 34 per cent, glucose, 27 per cent; pyruvate, 5 per cent. But the extraction of these substances was related to the arterial level with the heart metabolizing the substrates most readily available In starving animals, the cardiac R.Q falls to 0 70, indicating that fats are utilized almost exclusively. It has been reported[37] that a sex difference in coronary flow exists, with coronary flow per unit weight of the left ventricle being approximately 25 per cent greater in women than in men, associated with increased oxygen consumption of left ventricular muscle of the female heart and accompanied by decreased efficiency (see TABLE 2). Support for this observation is found in the fact that (1) testosterone may decrease oxygen consumption of tissue slices from several organs of rats, (2) the coronary arteries of male babies have a thicker intima and smaller lumen than those of female babies; (3) the ratio of coronary artery circumference to heart weight may be greater in the adult human female than the male[13]; (4) in humans under 40 years of age there is a decidedly greater incidence of coronary artery occlusion in the male than the female and (5) smaller dogs are reported to have a higher coronary blood flow and oxygen consumption per unit weight of heart than larger dogs, apparently as a result of the difference in heart weight The female human heart, being smaller, may have greater flow with an increased oxygen consumption per unit weight.

There has been considerable speculation for many years as to the controlling mechanism for coronary flow[18] Some investigators have believed that the blood vessels are essentially passive, with flow depending on the perfusing pressure and the varying resistance to flow through the coronary circuit, depending on the state of contraction of the myocardium Certainly, it has been adequately demonstrated that with constant aortic pressure, coronary flow consistently increases during asystole. Others have felt that the coronary vessels themselves are active in control of flow through their lumina, their size varying in relation to nervous control or to more direct humoral stimulation from variation in the quantity of oxygen utilized or metabolites produced in the heart muscle. Although considerable evidence has been marshalled in support of one or another of these concepts to the exclusion of others, it would appear more reasonable to postulate that mechanical, nervous, humoral and perhaps hormonal influences interact in this control

Since 1885, when Yeo demonstrated to his

own satisfaction that the resting heart consumed about one-sixth as much oxygen as the beating heart, it has been known that the oxygen consumption of the heart may be divided into two portions or phases. that pertaining to requirements for external work, and that required for maintenance and metabolism of the myocardial structure Under conditions of cardiac arrest, when coronary perfusion pressure is artificially maintained, the myocardial oxygen consumption rises transiently and then drops precipitously to about 30 per cent of that of the normally working heart [26] The fact that the myocardial oxygen consumption rises early and does not decline to a stable basal level for at least 25 to 30 seconds after cessation of cardiac contraction has been thought to indicate that an oxygen debt may be contracted by the left ventricle and satisfied during the period of rest [26] During ventricular fibrillation or while the beating heart is empty, the useful work of the heart falls to zero Under these circumstances, the oxygen consumption is 50 to 60 per cent below that of the normally beating heart.[34] The resting perfused dog heart consumes about 2 0 cc O_2/100 Gm /minute,[26] and with some reservation this figure may be compared with the oxygen consumption of direct myocardial biopsies taken from living dogs In these studies, oxygen consumption is roughly 1 1 ml./100 Gm /minute for the needle biopsy specimens and 1 7 ml /100 Gm /minute for myocardial slices incubated in a Warburg apparatus Certainly the oxygen consumption of myocardial slices compares very favorably with that of the isolated perfused myocardium

Physiologic variations in coronary flow have been extensively investigated in experimental animals and to some extent in man Available data indicate that coronary blood flow decreases during hypothermia, but not to the same extent as the cardiac output; hence, the fraction of cardiac output perfusing the coronary vessels is increased [44] Cardiac oxygen consumption moreover is greatly reduced by hypothermia, but since cardiac work decreases more than cardiac oxygen consumption, efficiency falls. During hyperthermia, coronary flow increases and the per cent of cardiac output which perfuses the coronary vessels also increases Here, as opposed to hypothermia, the myocardial oxygen consumption is greater than normal. Since cardiac work does not rise proportionately, the myocardial efficiency falls. It has not been possible as yet to differentiate the efficiency associated with the increase in cardiac rate which accompanies hyperthermia from that related to other factors.[31] Utilizing the Langendorff perfusion of the dog's heart, it has been shown that cardiac oxygen consumption and heart rate are linearly related, and by extrapolation to zero it was concluded that the resting heart should consume 1 98 cc. O_2/minute/100 Gm of muscle,[49] a figure which checks remarkably well with that established by actual measurements [26] Not only is acceleration accompanied by increased myocardial oxygen consumption, but cardiac efficiency falls since the amount of external work accomplished does not rise proportionately [30] Production of A-V block in dogs with its coincident decrease in heart rate has been associated with increased myocardial efficiency. The observations on the direct relationship of cardiac oxygen consumption and rate coincide with the thesis that the parameter most directly related to oxygen usage is the length of time the heart is in systole and the tension it develops during systole [43] Since the resting myocardial oxygen consumption represents essentially a fixed value, the more work the heart performs, up to a critical point, the greater is the cardiac efficiency. Stimulation of the stellate ganglion of the sympathetic nervous system in the dog causes a marked increase in the vigor of cardiac contraction accompanied by increased cardiac work, increased coronary flow and myocardial oxygen consumption [48] These effects are similar to those of epinephrine There are other interesting aspects Stimulation of the peripheral end of the cut vagus nerve reduces coronary flow [18] When the work load of the left ventricle is increased by clamping the aorta proximal to the orifices of the coronary vessels, coronary flow and myocardial O_2 consumption increase [21] The coronary blood flow and cardiac efficiency of man increases in response to exercise.[25]

Investigation of coronary blood flow has been carried out in various pathologic condi-

tions as well as in the fields of experimental medicine Results available indicate that in human cardiac failure, coronary blood flow is slightly reduced and oxygen extraction slightly increased, but myocardial consumption per unit weight of left ventricle are normal for oxygen, carbon dioxide, glucose, lactate, pyruvate, fatty acids, amino acids and ketones.[5] However, when consideration is given to the usual cardiac hypertrophy and increased heart weight, there is noted a decrease in the amount of work performed per unit of oxygen consumed and a decrease in cardiac efficiency.[5] Subsequent to treatment with digitalis, the efficiency of the recompensated heart becomes more nearly normal [6] In anemic states, there is a considerable increase in coronary blood flow, and with elevation of the hemoglobin by transfusions of blood these abnormalities tend to disappear [23] Thyrotoxicosis is accompanied not only by an increase in coronary blood flow per unit weight of myocardium but also an increase in cardiac oxygen consumption [24, 42] Myocardial metabolism of glucose, lactic acid and pyruvic acid do not differ from normal [24] After treatment and restoration of the euthyroid state, abnormalities of both coronary flow and oxygen consumption return to normal [42] Patients with mitral stenosis have shown a variable decrease in coronary blood flow per unit weight, possibly as a result of variable restriction of the blood flow at the mitral orifice with a decrease in cardiac output, left ventricular work and left ventricular myocardial oxygen consumption.[40] In aortic insufficiency with heart failure, myocardial oxygen consumption is increased but, when angina coexists, there is a reduced coronary flow and myocardial oxygen uptake [10] With arteriosclerotic heart disease producing angina pectoris, the coronary blood flow and myocardial oxygen consumption are essentially normal, however, there is evidence indicating that the coronary blood flow does not increase in response to nitroglycerine as it does in normal individuals.[17] From these data it has been concluded that in subjects with angina pectoris the vessels of the myocardium are unable to dilate satisfactorily to allow an increase in coronary flow and that nitroglycerine relieves anginal pain by causing a decrease in the left ventricular work.[17] In hypertensive cardiovascular disease, coronary blood flow and oxygen consumption per 100 Gm. of myocardium appear within normal limits.[4, 40] It has been extrapolated from these data that the myocardial weight is directly related to the amount of work required of the heart, and hence the metabolism per unit weight can remain normal.[4] Since Wearn has shown a decrease in the number of capillaries per cross section area of muscle in hypertrophied hearts, it may be assumed that a greater flow occurs per capillary and coincidently more resistance to flow, since a higher perfusion pressure accomplishes only an equal amount of flow per unit weight In coarctation of the aorta, on the other hand, coronary flow is reported to be increased disproportionately and myocardial oxygen consumption increased, while coronary vascular resistance is normal [4] These observations are in accord with the hypothesis that, at least in younger subjects with coarctation of the aorta, the increased resistance to flow is localized to the area of constriction of the aorta, but in other varieties of hypertension the increased vascular resistance is distributed throughout the body in the arterioles In cor pulmonale, coronary blood flow per unit weight of left ventricle appears normal[35]; this should be compared with observations in the dog indicating that elevated pulmonary artery pressure is accompanied by a slight increase in left and a greater increase in right coronary flow.[20] During hypotension and "shock" the cardiac output and coronary blood flow of the dog are sharply reduced,[46] but coronary blood flow does not fall proportionately Indeed, it is only in the later stages of "shock" that cardiac insufficiency is attributed to inadequate coronary flow, and effectively relieved by increased coronary perfusion [46]

Existing methods of determining coronary blood flow have been particularly suitable for studying the effects of various drugs on coronary blood flow and systemic hemodynamics Although there is considerable deviation from subject to subject insofar as coronary flow is concerned, the variations from time to time in the same resting individual are distinctly less

striking.[41] Therefore, it is possible to use each individual or animal as his own control, providing the drug to be administered acts within a reasonably short period of time and produces a steady state for proper hemodynamic measurement. As a result of these considerations, certain data have been accumulated concerning the action of drugs on coronary flow and myocardial metabolism. The following table (TABLE 3) has been adapted from Gregg,[19] to summarize diagrammatically information concerning drugs.

TABLE 3—*Action of Drugs on Coronary Flow and Myocardial Metabolism*

Drug	Subject	Left cor flow	O_2 extracted	O_2 used	LV work	LV effic
Epinephrine[3, 19]	Dog	↑	↑	↑	↑	↓
Norepinephrine[3]	Dog	↑	↑	↑	↑	↓
Mephenteramine[50] (Wyamine)	Dog, normal	↑	?	↑	↑	↓
Mephenteramine[50]	Dog, failed heart	↑	?	↑	↑	↑
Phenyl-2-butyl norsuprifen-HCl[29] (Arlidin)	Dog	↑	↑	↑	↑	↓
Coramine[19]	Dog	↑	↑	↑	↑	↓
Aminophyllin[19]	Dog	↑	↑	↑	↑	↓
Aminophyllin[9, 32]	Man	↓	↑	→	↓	↓
Nitroglycerin[17, 19]	Dog, man, normal	↑	↓	→	↓	↓
Nitroglycerin[17]	Man with angina	→	→	→	↓	↓
Papaverine[19]	Dog	↑	↓	?	↓	?
Atropine[16]	Man	↑	↑	↑	→	↓
Khellin[29]	Dog	↑	↑	↑	↑	↓
Nikethamide[12]	Dog	↑	?	↑	↑	↓
Urine[47]	Dog	↑	↓	→	?	→
Smoking[2] (nicotine)	Man	↑	↓	→	↓	↓
Strophanthus[6]	Man, normal	→	→	→	↓	↓
Strophanthus[6]	Man, failed heart	→	→	→	↑	↑
Quinidine[29]	Dog	↑	↑	↑	→	↓
Salicylate[43]	Dog	→	↑	↑	→	↓
Serotonin[27]	Dog	↑	↓	→	↓	↓
1-Hydrazinophthalazine[41] (hydrallazine)	Man	↑	↓	→	→	→
Hexamethonium[11]	Dog	↓	↑	→	↓	↓
Mecamylamine[35]	Dog	↓	↑	→	↓	↓
Chlorpromazine[26]	Dog	→↓	↑	→	↓	↓
Hypercapnia[14]	Dog	↑	↓	↑	?	→
Hypoxia[19]	Dog	↑	↓	→	→	→

It should be emphasized, in determining whether or not a drug is desirable for its effects on the myocardial circulation, that more should be considered than merely an increase or a decrease in the amount of blood which flows through the coronary vessels. One must also consider whether the increase in flow is accompanied by an increase in cardiac oxygen consumption, if the work of the heart will be increased or decreased and whether the cardiac efficiency is improved or made worse. Gregg[19] has referred to those substances which cause dilatation of the coronary vessels accompanied by an increase in the coronary sinus oxygen content with an unaltered or decreased oxygen consumption of the heart as "benign" coronary vasodilators. On the other hand, he refers to those substances which cause increased coronary blood flow accompanied by an increase of cardiac oxygen consumption and a decrease in the coronary sinus oxygen content as "malignant" coronary dilators. It is readily apparent that such a designation is a useful clinical index concerning drugs since the so-called "benign" group tends to increase the over-all myocardial oxygen tension and, therefore, permits the heart to function on a wider margin of safety insofar as oxidative metabolism is concerned, whereas the "malignant" group may actually be harmful. It should be considered on this basis that, although certain widely used drugs produce coronary vasodilatation, they may do so to the detriment of the heart muscle rather than to its benefit. In this group might be listed the various sympathicomimetic amines (epinephrine, norepinephrine and mephenteramine) as well as aminophyllin, Coramine, khellin, quinidine, Arlidin and salicylate. On the other hand, drugs which should be beneficial to the myocardium are nitroglycerin, serotonin, the active pharmacologic agent in urine and, insofar as is known papaverine. The increase in coronary flow with these drugs is accompanied by an increase in the coronary sinus oxygen content, with no particular change or actual reduction in the amount of left ventricular work.

Even though experimental data on a given drug indicate it belongs to the "benign" group of dilators, there should be thoughtful d

tion in therapy. For example, even though experimental data for 1-hydrazinophthalazine (hydrallazine) appear satisfactory (Table 3), it should be emphasized that the drug may precipitate chest pain in patients with angina pectoris.[41] It may be postulated that this is due to the fact that the coronary arteries in cases of the anginal syndrome are so rigidly stenotic it may be impossible for a vasodilating drug to produce an increased coronary flow. Under these circumstances, the increase in cardiac work, which may sometimes occur on administration of hydrallazine, is met by relative inadequacy of coronary flow, and myocardial ischemia results. The fact that the ganglion blocking drugs, hexamethonium and mecamylamine have produced a decrease in coronary blood flow, does not necessarily mean that such drugs are detrimental to the myocardium since there is a significant reduction in cardiac work and coronary perfusion pressure after their administration, both factors are undoubtedly related to the decreased coronary flow.

The decrease in efficiency as manifested after administration of several of these drugs as described above, may be due to quite different mechanisms For example, the response to epinephrine may be related to its specific oxygen wasting effect on the myocardium[19] Quinidine, on the other hand, may decrease myocardial efficiency because of the marked increase in rate which occurred subsequent to its administration.[49] This demonstrates the rather non-specific adverse effect of an increase in rate on cardiac efficiency It has been demonstrated in the heart-lung preparation, in the isolated metabolically supported heart and in the intact dog that cardiac efficiency is related inversely to cardiac rate,[30] at least throughout that range from normal to tachycardia. Salicylates, on the other hand, have been shown experimentally to uncouple oxidative phosphorylation in a manner very similar to that of 2-4 dinitrophenol[7] This explains, apparently, why the administration of salicylates in large doses leads to increased myocardial oxygen consumption and decreased cardiac efficiency.[43]

In summary, it may be said that of the many methods for determining coronary blood flow each presents certain advantages and disadvantages. The N_2O method has received widest application in the intact animal and man Numerous investigations are now available which have covered the normal, various disease states, and the effects of the commonly used drugs which are given to influence systemic and coronary hemodynamics. Despite the many disadvantages of the methods currently in use, a considerable body of useful information has been obtained With improved methods, it is anticipated that the existing information can be re-evaluated and supplemented to fill the many gaps in our present knowledge.

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Nikethamide[12]	Dog	↑	?	↑	↑	↓
Urine[47]	Dog	↑	↓	→	?	→
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Strophanthus[6]	Man, normal	→	→	→	↓	↓
Strophanthus[6]	Man, failed heart	→	→	→	↑	↑
Quinidine[39]	Dog	↑	↑	↑	→	↓
Salicylate[43]	Dog	→	↑	↑	→	↓
Serotonin[27]	Dog	↑	↓	→	↓	↓
1-Hydrazinophthalazine[41] (hydrallazine)	Man	↑	↓	→	→	→
Hexamethonium[11]	Dog	↓	↑	→	↓	↓
Mecamylamine[35]	Dog	↓	↑	→	↓	↓
Chlorpromazine[28]	Dog	→↓	↑	→	↓	↓
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sympathin E as the excitatory substance and sympathin I, the inhibitory substance, and developed the theory that sympathin (epinephrine or an epinephrine-like substance) combines in the effector cell with either an inhibitor (I) substance to form sympathin I or with an excitor (E) substance to form sympathin E

In recent years this concept has been questioned and new theories advanced which suggest (a) that more than one substance is released from postganglionic sympathetic nerve fibers and (b) that there may be more than one type of receptor in the effector organ. Until more evidence is available, these conflicting concepts cannot be resolved

Whatever theory is used to explain the mediation, the response to sympathetic stimulation results in vasodilatation of the arterioles supplying the muscles, and vasoconstriction of certain other vessels, as for example, those of the skin and splanchnic viscera.

Acetylcholine is found in the ganglia at the junctions of the preganglionic and postganglionic neurons This substance is necessary for impulse transmission from preganglionic to postganglionic fibers Since cholinesterase is also present in these tissues, the action of acetylcholine is readily regulated Experimentally, ganglia can be stimulated by acetyl-β-methylcholine and inhibited by anticholinergic drugs such as β-diethylaminoethyl xanthene-9-carboxylate methobromide (Banthine) Physostigmine salicylate can block cholinesterase activity by binding the cholinesterase molecule with a resultant increase in the concentration of acetylcholine Vasodilatation is produced because of a direct dilating effect of the acetylcholine on the smooth muscle cells of blood vessels

The posterior lobe of the pituitary gland produces pituitrin which, if injected, results in vasoconstriction by acting directly on the blood vessels. The nasal inhalation of this agent also results in vasoconstriction. This substance is used at times for the treatment of erythermalgia

Thyroid extract, thyroglobulin (Proloid) and triiodothyronine (Cytomel) all produce vasodilatation if adequate doses are administered Vasodilatation is prominent in patients with hyperthyroidism, whereas vasoconstriction occurs commonly in patients with hypothyroidism

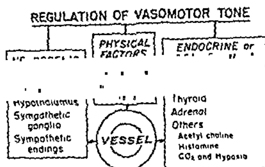


Fig 1—Common factors which alter vasomotor tone The tone may also be altered by disease or drugs.

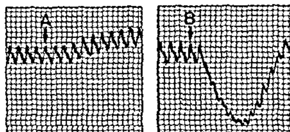


Fig 2—Plethysmograms made from the tip of the finger (A) Patient voluntarily thinks of a pleasant situation (B) Patient voluntarily thinks of an unpleasant situation. Vasoconstriction fails to occur in the former case, however, in the latter case the sympathetic nervous system is stimulated, resulting in constriction of the finger-tip

Histamine is liberated locally by injured tissues and results in capillary dilatation. Ischemia of muscular tissue liberates metabolites which have a profound vasodilating effect. Usually, vasodilatation is local, but if sufficient vasodilating substances are released, a general effect may occur Certain other tissues produce vasoconstricting substances when ischemia is present Renal ischemia characteristically produces a substance which combines with chemical agents from the liver to form angiotonin which is a vasoconstrictor

Physical Factors Regulating Vasomotor Tone

The environmental temperature has a profound effect on the vasomotor tone in the acral portions of the body. The changes occur in an effort to maintain a constant temperature in

Peripheral Vascular Dynamics as Related to Circulatory Efficiency

By TRAVIS WINSOR, M D.

Assistant Clinical Professor of Medicine, University of Southern California, School of Medicine, Director, Heart Research Foundation, Los Angeles, California

Dynamics of the Normal Circulation

An efficient peripheral circulation is essential for the proper nourishment of the body This requires a complex system consisting of the various mechanisms necessary for regulation of the heart rate, stroke volume and control of the caliber of peripheral blood vessels The ultimate purpose of these mechanisms is to deliver nutritional substances across the capillary membrane to the cells and to return products of cellular metabolism to the blood by the same route This chapter emphasizes those factors which affect the peripheral blood vessels, since the central control of the circulation is discussed elsewhere

Physiologic Factors Affecting Peripheral Blood Flow

The peripheral vessels normally are in a state of partial vasoconstriction which is called vasomotor tone This vasomotor phenomenon at any moment is the result of numerous vasodilating and vasoconstricting factors and represents a balance of forces which are of nervous, endocrine, hormonal, metabolic, local and environmental origin (Fig 1) This tone may also be modified with drugs and by disease

Nervous Factors Regulating Vasomotor Tone

The cerebral cortex often effects changes in vasomotor tone. It is well known that patients with anxiety states characteristically have cold, wet extremities, while calm, relaxed individuals have extremities which are often warm and dry The influence of the cerebral cortex on peripheral circulation may be demonstrated plethysmographically by measuring the pulsations and the total volume of the finger tip while a subject thinks of a pleasant or an unpleasant situation (Fig 2). Pleasant thoughts promote vascular relaxation, while unpleasant thoughts induce vasconstriction. The emotional response to an environmental situation may also alter vasomotor tone This may be demonstrated by a patient who looks alternately at two Rorschach cards while the vasomotor reactions at the finger tip are being measured plethysmographically One card may evoke no vascular response since the ink blot on the card has produced no emotional change. The other card may result in vasoconstriction because this ink blot has suggested an unpleasant experience Most emotional disturbances promote vasoconstriction of the digits and ears An exception is embarrassment which produces constriction of the digits with vasodilatation in the ears and blush areas Fear produces dilatation in certain muscular areas and constriction in the digits

Hormonal and Local Chemical Factors Affecting Vasomotor Tone

Some of the endocrine and local chemical agents affecting vasomotor tone are norepinephrine, epinephrine, acetylcholine, cholinesterase, thyroglobulin, pituitrin and histamine Norepinephrine is a powerful vasoconstrictor of skin vessels and is more potent in this regard than epinephrine Epinephrine is the principal substance produced by sympathetic stimulation of the adrenal medulla, it is known that the adrenal medulla also elaborates norepinephrine Epinephrine induces vasodilatation in certain areas as in muscle, and vasoconstriction in other areas including the skin The theory of sympathins I and E was proposed to explain how stimulation of the sympathetic nervous system can result in vasoconstriction in one area and vasodilatation in another area Cannon and Rosenblueth suggested the terms

contrast, the blood vessels of the skin are influenced to a lesser extent either by ischemia or the metabolic products of muscular exercise; but they are markedly affected by sympathectomy. Painful stimuli and nicotine decrease skin flow without appreciably altering muscle flow, whereas epinephrine or 10 per cent oxygen favor a decrease in skin circulation but an increase in muscle flow (Fig. 4). Sympathetic blocking agents such as trimethidinium methosulfate, the hydrogenated ergot alkaloids (Hydergine), body heating, sympathetic block or spinal anesthesia increase the blood flow through the skin without significantly altering the muscle circulation. Tolazoline (Priscoline) characteristically increases the blood flow to the skin more than to the muscle. It is apparent that procedures which block the sympathetic nervous system exert a more profound dilating effect on the circulation of the skin than on muscle circulation.

	BLOOD FLOW	
	SKIN	MUSCLE
Smoking Pain	−	0
Hypoxia (10% O_2) Epinephrine	−	+
Alcohol Body heating Sympathetic block Spinal anesthesia Hydrogenated ergot alkaloids Tetraethylammonium	+	±
Exercise Direct limb heating Metabolites	±	+ +

Fig. 4.—Effect of certain drugs and procedures on skin and muscle flow. The skin flow was measured through the toe using a digital plethysmograph and the muscle flow through the calf using a calf muscle plethysmograph. It is apparent that skin and muscle flow may be concordant or discordant. The sympathetic blocking drugs and procedures influence skin flow primarily while exercise and metabolic products influence muscle flow primarily. (0 indicates no change in flow, − indicates a decrease in flow, + indicates an increase in flow, ± indicates a variable effect on flow.)

Nutritional Circulation and Shunt Circulation

The skin of the acral portions of the body is richly supplied with arteriovenous shunts. When these are closed completely, all blood flow is directed through the capillary circulation which provides nutrition to the tissues. When the shunts are widely open, the major portion of blood flows through the A-V anastomoses so that nutrition of the tissues is inhibited. Similar mechanisms may be present in muscle as well. Blood flow measurements by venous occlusion plethysmography, combined with simultaneous studies of the clearance of radioactive materials from skin or muscle, provide important information for distinguishing shunt from nutritional circulation. At least one such study suggests that sympathectomy increases shunt flow to the skin of the feet without a significant increase in the nutritional circulation.

The interchange of nutrients between capillary blood and interstitial fluids is the most important function of the circulatory system. The process follows certain known laws, as emphasized by Starling, yet further elucidation relative to capillary action is required. Starling has mentioned that to avoid swelling or shrinking of tissues, fluid must flow from the capillaries into the interstitial spaces and back again in equal amounts. This is accomplished primarily through a balance of hydrostatic and colloid osmotic pressures (Fig. 5). At the arteriolar end of the capillary the intravascular pressure exceeds that of the extravascular pressure and fluid flows from capillary to interstitial spaces. At the venular end of the capillary loop the tissue fluid forces exceed those of the intravascular forces and fluid flows from tissue spaces to blood vessels. In order to accomplish this interchange of fluid from vessel to tissue spaces and back again, two forces are required. First is the *filtration force* which forces fluid from the arteriolar end of the capillary into the tissue spaces. The filtration force is the difference in pressures between (a) the sum of the tissue colloid osmotic pressure and the capillary hydrostatic pressure and (b) the sum of the tissue hydrostatic pressure and the capillary colloid osmotic pressure. The second is the *reabsorption force* which forces fluid from the tissue spaces into the venular end of the capillary. This reabsorption force is the difference in pressures between (a) the sum of the tissue hydrostatic pressure and the capillary colloid osmotic pressure and (b) the sum of the

the body When the subject is put into a cool environment, vasoconstriction occurs in the digits and heat loss is prevented. Plethysmographic records made at this time from the digit show pulse waves and slow waves of low amplitude When the subject is placed in a warm environment, the digits become warmer and the vasomotor tone decreases The pulse waves and slow waves vary in size representing periods of vasodilatation alternating with periods of vasoconstriction as the body attempts to maintain a constant temperature When the body becomes hot, the pulse waves are larger, but the slow waves disappear due to a constant state of vasodilatation Under these conditions, the maximum amount of heat is lost from the skin (Fig 3) The direct application of heat or cold produces local circulatory changes as it alters the amount of vasodilator metabolites Local applications of heat or cold also may exert an indirect influence on distant parts of the body. If, for example, an arm is placed in hot water, vasomotor changes will occur in the leg as well as in the arm Here, it is believed that changing the temperature of the circulating blood modifies the sympathetic vasoconstrictor tone because of the effect of the warm blood from the heated arm on the brain If a tourniquet is placed on an arm and the arm is immersed in hot water, vasomotor changes at the toe do not occur until the tourniquet is released, allowing the warm blood to reach the brain

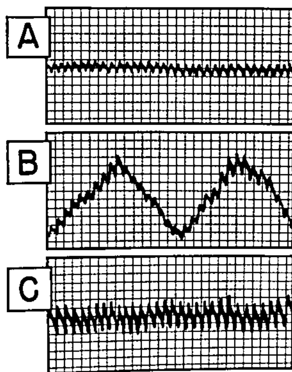


Fig. 3—Plethysmograms recorded from the tip of the finger. (A) Body cool, pulse waves and slow waves are of low amplitude, (B) Body warm, pulse waves are of increased amplitude and the slow waves are large, indicating periods of vasoconstriction alternating with periods of vasodilatation (C) Pulse waves are of large amplitude and the slow waves are of small amplitude This indicates that the vascular system is wide open and that vasomotor tone is constant and minimal

The Effect of Drugs on the Regulation of Vasomotor Tone

The peripheral circulation is influenced by many drugs which are relatively specific in their site of action. Many phenothiazine derivatives and perhaps certain of the barbiturates act on the higher centers of the brain The DH alkaloids of ergot (Hydergine) appear to act on the hypothalamus. The ganglionic blocking agents, mecamylamine (Inversine), chlorisondamine (Ecolid) and trimethidinium methosulfate, act on sympathetic and other ganglia Dibenzyline and phentolamine (Regitine) are adrenergic blocking agents and as such inhibit the action of epinephrine on the blood vessel Also, β-pyridyl carbinol (Roniacol), alcohol and tolazoline (Priscoline) have a direct action on the vessels themselves Some of these drugs, such as Priscoline, have multiple sites of action and for this reason are especially valuable for the treatment of peripheral vascular disease

Vasomotion in Muscle and Skin

Skeletal calf muscle contains about 10 times more capillaries than the skin of the toes Under conditions of rest many of the capillaries are nonfunctioning or they may transport only small amounts of blood. Muscle capillaries have only a few sympathetic nerves compared with the numerous sympathetic fibers supplying the vessels of the skin of the toes The blood vessels of the muscle dilate readily when there is an accumulation of metabolites secondary to exercise or ischemia. The blood flow to the calf muscle may increase 20 times to meet the metabolic needs of the exercising tissues In

contrast, the blood vessels of the skin are influenced to a lesser extent either by ischemia or the metabolic products of muscular exercise; but they are markedly affected by sympathectomy. Painful stimuli and nicotine decrease skin flow without appreciably altering muscle flow, whereas epinephrine or 10 per cent oxygen favor a decrease in skin *circulation* but *an* increase in muscle flow (Fig 4) Sympathetic blocking agents such as *trimethidinium methosulfate*, the hydrogenated ergot alkaloids (Hydergine), body heating, sympathetic block or spinal anesthesia increase the blood flow through the skin without significantly altering the muscle circulation. Tolazoline (Priscoline) characteristically increases the blood flow to the skin more than to the muscle. It is apparent that procedures which block the sympathetic nervous system exert a more profound dilating effect on the circulation of the skin than on muscle circulation

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CAPILLARY		
ARTERIOLAR LIMB	LOOP	VENULAR LIMB
Outflow Forces. TCOP + CHP *Inflow Forces* THP + CCOP *Difference* = FILTRATION FORCE	*Outflow Forces* TCOP+CHP *Inflow Forces* THP + CCOP FORCES ARE EQUAL	*Inflow Forces:* THP + CCOP *Outflow Forces* TCOP + CHP *Difference* = REABSORPTION FORCE

FIG 5—The forces which are present at the arteriolar limb of the capillary, capillary loop and venular end of the capillary are responsible for the filtration of fluids out of the arteriolar capillary limb into the tissue spaces and for the reabsorption of fluids from the tissue space into the venular end of the capillary (From WINSOR, T Peripheral Vascular Diseases, an Objective Approach Springfield, Ill, Charles C Thomas, 1959)

tissue colloid osmotic pressure and the capillary hydrostatic pressure At the capillary loop the pressures on the two sides of the capillary wall are equal so that no exchange of fluid takes place.

ALTERED VASOMOTOR TONE BECAUSE OF CONDITIONING

Vasoconstriction is produced through the mechanism of conditioning, a mechanism which may be studied in the toe The examples are interesting A soft gentle sound for three seconds in most subjects fails to produce a vasoconstriction, but an electric shock applied to the skin of the arm generally produces definite general vasoconstriction After the sound and shock have been administered together for 10 times, the sound alone then produces vasoconstriction. It is probable that vasomotor tone is altered significantly and repeatedly throughout the day because of previous conditioning It is also possible that certain disease states, such as Raynaud's disease, represent abnormalities of the conditioning process in which the conditioning of vasoconstriction of the digits occurs too easily, lasts too long, or is transferred too readily from one stimulus to another

PHYSICAL FACTORS AFFECTING PERIPHERAL BLOOD FLOW

It is axiomatic that knowledge of physical hydraulic principles assists in understanding the physiology of the human circulation The principles governing the flow of fluids in straight, rigid tubes are well known, and these principles, with modifications, may be applied to blood flow in the vessels of man even though the vessels may be tortuous, conical or elastic. There are numerous factors which must be considered when dealing with circulatory dynamics These take into consideration the vessels themselves, the blood flowing through the vessels, the pressures which move the blood and finally the mechanisms by which the nutritive material of the blood reaches the tissues

Blood Flow

The volume of blood flowing in a vessel per unit of time is usually designated by the letter *Q* (FIG 6) and is expressed in milliliters or liters per minute In adults, the blood flow is approximately 5 L per minute For example, the left ventricle pumps 5 L in one minute and this amount of blood traverses each section of the vascular system, i e , 5 L per minute pass through the aortic section, through the large branching arteries, through the arterioles and finally traverse the capillaries, venules and venous plexuses, large veins, inferior vena cava, right auricle, right ventricle, lungs and left auricle In general, the blood flow is determined by the blood pressure difference between two points, the viscosity of the blood, the length and radius of the vessel and by other factors. These relationships may be studied by employing a standard model which consists of a reser-

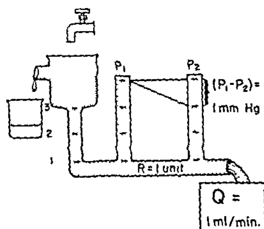


Fig 6—Standard model used for studying blood flow P_1 and P_2 are manometers called Pitot tubes Q is the volume rate of blood flow measured in milliliters per minute R is the resistance measured in units

voir into which water is directed (Fig. 6). The reservoir contains a spillway so that a constant head of pressure is maintained in the system. The head of pressure may be altered by raising or lowering the reservoir. The rate of flow is measured by collecting the water in a graduated cylinder after it has flowed through the system for a particular time interval With this model the diameter and length of the tube through which fluid flows can be varied, and fluids of different viscosities may be employed.

Blood Pressure

The blood in a given vessel exerts pressure (*P*) in a forward and a lateral direction The pressure may be measured in the horizontal portion of the tube with manometers (Pitot tubes) inserted into the system (Fig 7). One manometer with straight sides arises from the lateral wall of the vessel and another manometer with a curved tip arises from the lumen of the vessel The lateral pressure is measured by the height of the fluid column in the straight tube; the forward pressure is derived by taking the difference in the heights of the fluid columns in the two tubes. As the velocity increases, the forward pressure increases and the lateral pressure decreases. When the velocity decreases, the lateral pressure increases and the forward pressure decreases When there is no fluid flow in the tube, pressure is exerted in a lateral direction entirely and the pressure is zero

Resistance to Flow

Resistance is the opposition to flow and depends on a variety of factors including the cross sectional area, length of the tube and the viscosity of the fluid. The peripheral resistance unit (1 PRU) is the resistance noted when there is a flow of 1 ml. per minute and a pressure difference of 1 mm. Hg between the two ends of the tube through which the fluid passes (Fig. 6).

Flow, Pressure and Resistance

The following formula pertains to the relationship of three important factors involved in the circulation of the blood:

$$Q = \frac{P_1 - P_2}{R} \qquad (1)$$

Q = flow,
R = resistance
$P_1 - P_2$ = the difference in height between the two fluid columns in the manometers which are inserted into the horizontal tube or blood vessel

It is evident that the blood flow (Q) is increased when the numerator is increased with respect to the denominator, i e , when the pressure difference is increased with respect to the resistance The greatest change in flow, of course, would occur if the pressure difference were increased and the degree of resistance lowered If, employing the model, the head of pressure were raised by increasing the height of the reservoir above the horizontal tube and at the same time the horizontal tube were increased in diameter, the numerator would in-

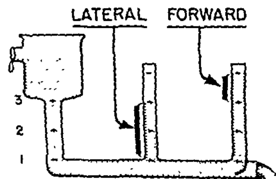


Fig 7—Types of manometer tubes used for measuring lateral and forward pressure The straight tube measures lateral pressure The tube with the curve at the tip assists in measuring forward pressure

crease at the same time the denominator decreased so that the blood flow (Q) would rise significantly.

In studying the peripheral circulation in man it is possible to measure the blood pressure at various sites on a limb This is done usually for the purpose of locating obstructions in the arterial tree To understand the factors which alter the pressure drop between two points on a horizontal tube or a blood vessel, the formula may be rearranged as follows:

$$P_1 - P_2 = Q \times R \tag{2}$$

The formula indicates that the pressure difference between the two points can be elevated by increasing the rate of flow or the resistance or both Again, employing the model, this could be accomplished by raising the reservoir which increases the head of pressure and at the same time constricting the horizontal tube between the two points of measurement Under these circumstances a large pressure drop occurs because both Q and R would be increased

At times, it is important to measure the peripheral resistance which is a ratio between pressure drop and flow Here, the equation is rearranged again.

$$R = \frac{P_1 - P_2}{Q} \tag{3}$$

The factors which increase the pressure drop between two points or decrease the blood flow will cause an increase in peripheral resistance For example, a constriction imposed between the two manometers on the horizontal tube or blood vessel without changing the height of the reservoir would increase the resistance considerably.

Poiseuille put into mathematical terms the factors which determine the flow of fluids through tubes He observed that increased resistance to flow results from an increase in blood viscosity, increase in vessel length, a decrease in vessel diameter, or a decrease in the cross sectional area. Poiseuille's law states that the volume flow of fluid through a tube per unit of time is directly proportional to the difference between the pressure at the two ends of the tube in which fluid is flowing and to the square of the cross sectional area of the tube; and is inversely proportional to the length of the tube and the viscosity.

$$Q = \frac{(P_1 - P_2) \times A^2}{L \times \eta \times 8\pi} \tag{4}$$

$P_1 - P_2$ = pressure difference in dynes per square centimeter *
A = cross sectional area of the tube in cm^2
L = length of the tube in centimeters
η = viscosity in poises (dynes per second per square centimeter)
Q = flow in milliliters per second.
π = 3 1416

Since the cross sectional area (A) = πr^2 where r = the radius of the tube, equation no. 4 may be rewritten as follows:

$$Q = \frac{(P_1 - P_2) \times (\pi r^2)^2}{L \times \eta \times 8\pi} \tag{5}$$

Poiseuille's law expressed in this form emphasizes the importance of the radius of the tube (i e, blood vessel) since this equation indicates that doubling the radius of the tube will increase the flow 16 times. Contrariwise, 20 per cent reduction in the radius will result in a 59 per cent reduction in blood flow. Thus, it is apparent that tiny changes in the caliber of the smaller blood vessels may result in a large change in blood flow

Volume of Blood in Various Segments of the Vascular Tree

The volume of blood in each segment of the vascular tree may be estimated from the length of the various segments of the vascular tree, e g, the aorta, arterioles, etc., the diameter of the individual vessels, and the number of vessels in each vascular segment In adults approximately 4,082 ml of blood are present in the peripheral circulation (Fig 8); an additional 1,302 ml may be present in the heart and lungs. Over 50 per cent of the blood in the peripheral circulation is located in the venules, veins and vena cava. This large venous reservoir, which plays a significant role in the regulation of the circulation, may be increased by shock or by congestive heart failure.

* 1 mm of water pressure at 4 C is equal to a force of 98 0638 dynes per cm^2 Also, 1 mm Hg exerts a force of 13 6 × 98 0638 dynes per cm^2

Blood Velocity

The velocity of blood flow is the distance a unit of blood travels in a period of time. The velocity varies directly with the volume of blood flowing and inversely with the cross sectional area of a single vessel or the total cross sectional area of a vascular segment. The velocity of flow varies significantly in various segments of the vascular system; for example, with a cardiac output of 5,000 ml. per minute, which is 83 ml. per second, and with a cross sectional area in the aorta of 2.4 cm.^{2}, the velocity of blood flow in the aorta would be 35 cm per second (FIG 9). The velocities shown in FIGURE 9 were derived mathematically and are based on certain assumptions, but are believed to approximate the various velocities in a normal, resting adult. In general, blood travels more rapidly in the aorta than in any other vascular segment, and the velocity of flow decreases progressively from the aorta to the capillaries as the total cross sectional area increases. The blood velocity in the capillaries is slow, giving adequate opportunity for interchange of substances between the blood and tissue fluids When the blood reaches the large veins and inferior vena cava, the velocity increases because the total cross sectional area of these vessels is less than the capillaries.

Bernoulli observed that a slow blood velocity was associated with a high lateral and a small forward pressure. He also observed that decreasing the diameter of a tube increased the velocity of the fluid in the tube which decreased the lateral pressure and increased the forward pressure. He thus proposed a law stating that the lateral pressure varies inversely with the velocity He also stated that, disregarding the effects of friction at any point in a cylinder in which fluid is flowing, the sum of the lateral and forward pressure is constant. Bernoulli's equation is as follows:

$$P + HDg + \tfrac{1}{2}DV^2 = K \qquad (6)$$

P = pressure in mm Hg
H = height in centimeters fluid will rise in a tube above a reference plane
D = density of the liquid in grams per milliliter.
g = acceleration due to gravity (980 cm /second^2).
V = velocity of flow in centimeters per second

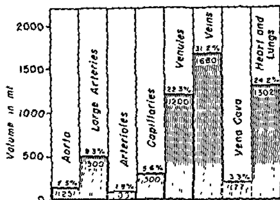


FIG 8—Volume of blood in various vascular beds.

	Velocity cm per second
AORTA	35
BRANCHING ARTERIES	3.3
ARTERIOLES	0.8
CAPILLARIES	0.04
VENULES	0.17
LARGE VEINS	1.0
VENA CAVA	24.4

(Scale: 0, 15, 35 — *Velocity cm per second*)

FIG 9—Approximate blood velocity in various portions of the vascular system

Tension on Blood Vessel Walls

The tension on the blood vessel wall varies significantly in large and small vessels and in vessels with high and low pressure (FIG. 10). For example, the tension in the aorta is high because the pressure is great and the diameter is large The tension here is 10,000 times greater than in the capillaries where there is a low pressure and a small diameter.

The tension law of Laplace is as follows:

$$T = P_1 - P_2 \times r \qquad (7)$$

T = dynes per centimeter length
$P_1 - P_2$ = pressure difference inside and outside of the tube or vessel in dynes per square centimeter.
r = radius in centimeters

The relationship between tension of a vessel wall and the diameter can be illustrated by a partially blown-up rubber balloon. Palpation of the expanded part of the balloon will re-

crease at the same time the denominator decreased so that the blood flow (Q) would rise significantly.

In studying the peripheral circulation in man it is possible to measure the blood pressure at various sites on a limb This is done usually for the purpose of locating obstructions in the arterial tree To understand the factors which alter the pressure drop between two points on a horizontal tube or a blood vessel, the formula may be rearranged as follows:

$$P_1 - P_2 = Q \times R \qquad (2)$$

The formula indicates that the pressure difference between the two points can be elevated by increasing the rate of flow or the resistance or both. Again, employing the model, this could be accomplished by raising the reservoir which increases the head of pressure and at the same time constricting the horizontal tube between the two points of measurement. Under these circumstances a large pressure drop occurs because both Q and R would be increased

At times, it is important to measure the peripheral resistance which is a ratio between pressure drop and flow. Here, the equation is rearranged again:

$$R = \frac{P_1 - P_2}{Q} \qquad (3)$$

The factors which increase the pressure drop between two points or decrease the blood flow will cause an increase in peripheral resistance For example, a constriction imposed between the two manometers on the horizontal tube or blood vessel without changing the height of the reservoir would increase the resistance considerably

Poiseuille put into mathematical terms the factors which determine the flow of fluids through tubes He observed that increased resistance to flow results from an increase in blood viscosity, increase in vessel length, a decrease in vessel diameter, or a decrease in the cross sectional area Poiseuille's law states that the volume flow of fluid through a tube per unit of time is directly proportional to the difference between the pressure at the two ends of the tube in which fluid is flowing and to the square of the cross sectional area of the tube; and is inversely proportional to the length of the tube and the viscosity.

$$Q = \frac{(P_1 - P_2) \times A^2}{L \times \eta \times 8\pi} \qquad (4)$$

$P_1 - P_2$ = pressure difference in dynes per square centimeter.*
A = cross sectional area of the tube in cm^2
L = length of the tube in centimeters
η = viscosity in poises (dynes per second per square centimeter)
Q = flow in milliliters per second
π = 3 1416

Since the cross sectional area (A) = πr^2 where r = the radius of the tube, equation no 4 may be rewritten as follows:

$$Q = \frac{(P_1 - P_2) \times (\pi r^2)^2}{L \times \eta \times 8\pi} \qquad (5)$$

Poiseuille's law expressed in this form emphasizes the importance of the radius of the tube (i e., blood vessel) since this equation indicates that doubling the radius of the tube will increase the flow 16 times Contrariwise, 20 per cent reduction in the radius will result in a 59 per cent reduction in blood flow. Thus, it is apparent that tiny changes in the caliber of the smaller blood vessels may result in a large change in blood flow.

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V = velocity of flow in centimeters per second.

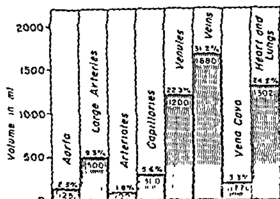


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Velocity cm per second (scale: 0, 15, 35)

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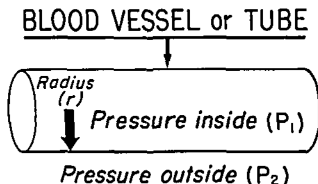


FIG 10—Factors which determine the tension on the wall of the blood vessel P_1 is the pressure inside of the vessel and P_2 is the pressure outside of the vessel and r is the radius

veal a tense wall Knowledge of the tension of the wall of the vessels takes on significance when considering the formation of aneurysms, the rapidity with which aneurysms enlarge once started and the possible relationship between high arterial pressure and the development of arteriosclerosis The pressure inside the balloon is the same where the diameter is large as where it is small, and the total force acting on the wall is proportional to the product of the pressure times the total area on which the force is acting ($F = PA$)

F = force in dynes
P = pressure in dynes per square centimeter
A = total area in square centimeters on which the force is acting
The surface area of a cylinder of length L is found from the equation $2\pi rL$
r = radius in centimeters
L = length in centimeters
π = 3 1416

Circulation Time

The circulation time is often difficult to evaluate clinically because it depends on two main factors, each of which is variable These factors are the volume of the vascular bed and the rate of blood flow The circulation time may be illustrated by the following formula:

$$t = v/Q$$

t = time in seconds,
v = volume of the system in milliliters
Q = flow in milliliters per second

The circulation time is increased when the numerator increases or the denominator decreases. A circulation time of 10 seconds might mean a vascular volume of 20 ml. and a blood flow of 2 ml. per second, or a vascular volume of 10 ml and a blood flow of 1 ml per second The circulation time is doubled, if either the rate of blood flow is halved where the volume remains constant or if the volume of the system is doubled when the flow rate is constant.

ADAPTIVE MECHANISMS IN VARIOUS CIRCULATORY DISTURBANCES

Shock

Shock is defined as a disturbance of fluid distribution resulting in a circulatory deficiency which is peripheral in origin From the standpoint of the clinical management of the patient, three main types of shock should be considered: (1) primary or initial shock, (2) shock due to hemorrhage and (3) traumatic shock

Primary shock This occurs frequently as a result of pain or fright and consists of the common "faint" The mechanism is probably due to general vasodilatation, neurogenic in origin The reaction occurs immediately after injury, it is transient, and characterized by a low arterial blood pressure, a weak pulse, muscular weakness and often sweating Capillary atony and endothelial permeability are not present and hence, there is no hemoconcentration

Shock due to hemorrhage This often resembles traumatic shock clinically but may be differentiated in that hemodilution occurs immediately after the hemorrhage, because tissue fluids rapidly enter the blood stream in order to replace the diminished blood volume The decrease in blood volume results in a series of events including decreased venous return to the heart, lessened arterial blood pressure, cardiac acceleration, arteriolar constriction with decreased renal flow, formation of angiotonin and decreased excretion of sodium, chloride and water Some of these events favor restoration of blood volume.

Traumatic shock This is characterized by endothelial damage and results in loss of fluid into tissue spaces with pooling of blood in

TISSUE ANOXIA
INJURIOUS AGENTS OR CONDITIONS
injury to other cells
electrolyte imbalance
low blood sodium, chloride bicarbonate
high blood potassium magnesium, calcium phosphate, sulfate
reduced delivery of O_2
abnormal catabolic products
endothelial injury
vasodilator products from liver, etc.
pathologic effects
capillary atony
dilatation
permeability
petechiae
stasis
fluid imbalance
edema
serous effusions
hemoconcentration
vasomotor failure (brain damage)
vascular damage (medial damage)
reduced volume flow
decreased blood volume
decreased venous pressure
decreased ventricular filling
decreased stroke volume
narrow pulse pressure
decreased arterial pressure
decreased glomerular filtration
decreased pressure in carotid sinus and aortic arch
decreased renal flow
decreased excretion sodium, chloride and water
sympatho-adrenal activity
arteriolar constriction
cardiac acceleration
discharge of venous reservoirs into vessels
liberation of epinephrine
angiotonin
production of renin
low capillary pressure

Fig 11 —Sequence of events which may occur in patients with shock (Adapted from Glasser, O Medical Physics Chicago, Yr Bk Pub, 1950, and Youmans, W B: Basic Medical Physiology Chicago, Yr Bk Pub 1952)

dilated capillaries The characteristic finding is hemoconcentration which often occurs before there is a fall of blood pressure The condition is slow in onset, and usually occurs several hours following injury.

In Figure 11 there is a portrayal of the adaptive mechanisms in traumatic shock. The process begins with injury to the endothelium due to various toxic agents or conditions; tissue anoxia, even moderate in degree, is regarded as distinctly harmful, also prolonged arterial occlusion is a detrimental factor. In addition, body cells may be implicated through an electrolyte imbalance due to loss of the osmotic characteristics of the cells This occurs when the cell membrane is changed from a normal semipermeable to an abnormal permeable one In the presence of a normal membrane and normal osmotic forces the cytoplasm contains an excess of potassium, magnesium, calcium, phosphates and sulphates as compared with the blood and tissue fluids, and the blood and tissue fluids contain sodium, chloride and bicarbonate in excess of that in the cytoplasm With cellular damage and destruction of the semipermeable membrane, these substances tend to occur in equal concentration in the cytoplasm and in the blood and tissue fluids

The pathologic effects of endothelial damage are capillary atony, characterized by dilatation of vessels, increased permeability, petechial formation, stasis and increased flow of lymph Fluid imbalance also occurs with edema, hemoconcentration, serous effusion and impaired absorption. The capillary damage, if severe, produces profound disturbances in the circulation. Damage to the vasomotor center in the brain favors peripheral vasodilatation and hypotension The hemoconcentration results in increased resistance, decreased volume flow, stasis and thrombosis. The decreased blood volume reduces the volume flow to the tissues, thus producing hypoxia with resultant tissue damage and the production of abnormal catabolic products.

Other manifestations of decreased blood vol-

ume are lowered venous pressure, ventricular filling and stroke volume. The diminished stroke volume results in a narrowed pulse pressure, manifesting itself clinically as a weak pulse and decreased arterial pressure A decrease in pressure in the cartoid sinus and in the aortic arch stimulates sympathoadrenal activity with cardiac acceleration, liberation of epinephrine and norepinephrine and discharge of blood into the circulation from venous reservoirs such as the spleen If the vasomotor system has not been damaged, there is arteriolar constriction which decreases renal blood flow and glomerular filtration rate, accounting for the oliguria or anuria as observed during shock

Renal ischemia in shock results in the production of the enzyme-like substance, renin. This influences pseudoglobulin in the blood to form angiotonin which results in further arteriolar constriction The arteriolar constriction produces a low capillary pressure which results in further tissue anoxia and subsequent cellular damage

Treatment Treatment of *primary shock* includes elevation of the patient's legs above heart level to favor venous return, aromatic spirits of ammonia to promote favorable vasomotor reactions, cool towels to the head, sedatives, reassurance and oxygen In most cases elevation of the legs is sufficient and recovery occurs within a few minutes. *Hemorrhagic shock* is treated by replacing blood. Traumatic shock, in its early stages may be improved with peripheral vasoconstrictors such as levarterenol, however, this form of treatment is unsuccessful in the presence of severe endothelial damage In animals during the early stages of shock, Dibenzyline, a vasodilator, has been used at times to decrease arteriolar constriction, thereby preventing cellular damage and the liberation of vasodilating catabolic products, the results have not been finally evaluated. When shock is initiated by heart failure, it is possible that agents with positive inotropic actions, such as mephentermine *(Wyamine), may* be of value When hemoconcentration is present, plasma transfusions are of inestimable value, especially if plasma loss is marked, as with burns

Orthostatic Hypotension

Orthostatic hypotension is a syndrome characterized by a fall in blood pressure when the patient stands a few seconds The condition may be associated with Addison's disease, diabetes mellitus, myasthenia gravis, nervous exhaustion and abnormalities of the sympathetic nervous system There is also an idiopathic condition known as primary orthostatic hypotension, associated with failure of the postural adaptive mechanisms Secondary postural hypotension may be due to (1) centrally acting drugs or cerebral disease, (2) drugs, surgery or disease-blocking sympathetic nerves, either in the spinal cord or peripherally, (3) abnormal pooling of blood in the venous reservoirs because of varicose veins or abnormal muscular support, such as is seen with myasthenia gravis, (4) a decrease in blood volume, such as after hemorrhage or with Addison's disease, (5) disease of the pressor receptors in the aortic arch or carotid sinus, such as thromboarteritis caroticosubclavia (Takayasu's disease) and (6) diseases of the heart which interfere with cardiac acceleration, such as complete heart block.

Primary orthostatic hypotension is characterized by a marked decrease of systolic and diastolic blood pressure on standing, often followed by syncope, failure of a normal increase in pulse rate, localized or generalized anhidrosis or hypohidrosis and secretion of increased quantities of urine in the supine as compared with the standing positions.

In normal subjects in the standing position, the pulse rate and systolic blood pressure increase about 10 per cent, while the diastolic pressure remains almost unchanged. Cardiac output remains constant or is slightly decreased in the standing position and consciousness is maintained The pressure at which unconsciousness occurs varies widely depending on the state of the cerebral vessels which determine the pressure required to perfuse the brain Normally, the blood pressure in the upright position is maintained by two major factors· (1) an increase in venoconstrictor tone and (2) cardiac acceleration. Failure of either of these mechanisms may result in postural hypotension These mechanisms are ac-

tive when the organs of adaptation are normal These consist of the baroreceptors (aortic arch and carotid sinus), afferent nerve pathways, cerebral vasomotor and cardiac regulator centers, efferent sympathetic cardiac accelerator and vasomotor nerves, normally responsive veins, normal blood volume and normal muscular support to the vessels.

In normal subjects, on standing, there is a transient drop in pressure in the carotid sinus and aortic arch which stimulates the vasomotor center, resulting in cardiac acceleration and venoconstriction The venoconstriction decreases the volume of the large venous bed and favors the return of blood to the right heart. The output of blood from the right heart is determined by the ability of the heart to pump blood away from the right atrium and ventricle and by the volume flow of blood into the right atrium. It is obvious that cardiac disease or valvular stenosis could interfere *with cardiac output and produce syncope.*

Certain observations may assist in revealing the mechanism of orthostatic hypotension in patients In normal persons, squatting slows the heart rate and standing increases the rate to a level greater than the initial standing control record During the Valsalva maneuver the pulse rate in the normal individual is slowed with straining but increases above the control level with the cessation of straining Normally, nitroglycerin accelerates the pulse and levarterenol slows the pulse

In patients with primary orthostatic hypotension, the overshoot reactions with squatting and standing and after the Valsalva maneuver *do not* occur and the pulse rate is not altered significantly by nitroglycerin and levarterenol. Vasoconstrictive mechanisms may be studied plethysmographically using a digital instrument In normal subjects, a sharp inspiration or painful stimulus to the skin elicits a sharp vasoconstriction lasting about a minute. Patients with primary orthostatic hypotension do not show these reactions nor do they exhibit the normal psychogalvanic skin reflex.

Treatment. The pressure may be elevated with the administration of mephentermine (Wyamine), ephedrine sulfate, paradrine or dextroamphetamine With these drugs, postural hypotension may still occur but syncope can usually be prevented, as the pressure may not fall below critical levels; also, a high sodium intake with trifluorocortisone acetate to facilitate sodium retention may be employed. A waist high elastic compression suit may be necessary.

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Functional Capacity and Exercise Tolerance in Patients with Impaired Cardiovascular Function

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From the Department of Clinical Physiology, Karolinska Sjukhuset, Stockholm, Sweden

IN patients with heart disease with manifest decompensation, the symptoms at rest usually provide sufficient guidance for evaluation of the functional impairment, but such evaluation is much more difficult in patients who are well compensated at rest.

The clinical findings such as auscultatory murmurs, roentgenologically demonstrable enlargement or deformation of the heart, or electrocardiographic changes, generally do not afford information on the degree of functional impairment. In many patients the history gives very incomplete information due to the fact that individuals are affected differently by certain limitations of functional capacity because of their individual habits of life, working conditions and environment. Therefore, a quantitative measure of the patient's working capacity, correlated with the physical qualifications otherwise should be of great value in preventing both overestimation of the functional significance of an easily demonstrable anomaly or impairment, and underestimation of a cardiac disease that superficially presents inconsequential objective changes A measure of the physical working capacity also is invaluable for objective follow-up evaluation of the course of a heart disease as well as the effect of operative or other treatment Such a measure should also aid in the social and vocational rehabilitation of the patient

A clinical test for working capacity also affords the possibility of observing abnormal reactions to exercise, which can contribute materially to the establishment of the correct diagnosis and to the explanation of the patient's subjective symptoms. Many patients have subjective and objective symptoms of their cardiac disease only in connection with physical exertion. In some patients, objective signs, e.g., those of coronary disease, can be demonstrated in the resting electrocardiogram, but frequently the response to exercise provides first definite evidence of the nature of the symptoms.

As might have been expected, there has been great interest in the development of methods for subjecting patients with heart disease to work tests, and many different procedures have been described. The various methods proposed will not be described in this paper. Instead, the writer will discuss the physiologic and pathophysiologic basis for application of exercise tests in the evaluation of cases of cardiac disease. Certain prerequisites for a clinical exercise test will be set up, and the writer's own experience with application of a procedure satisfying these conditions will be reported.

Physiologic Background

Introductory Definitions

The increased energy expenditure during bodily work places different demands on the organism according to the duration and type of the work. When the exercise is of very short duration, it can be carried out anaerobically and the oxygen requirements met afterward by balancing of the so-called oxygen debt. Accordingly, the muscular power that can be developed will determine the working capacity.

In the case of more prolonged work, i.e., with a duration of one minute or more, the magnitude of work performed becomes dependent on the quantity of oxygen that can be distributed to the working muscles in addition to the power that the muscles can develop. In work with small muscle groups, the quantity of oxygen taken up is determined primarily by

the musculature and its supply of blood vessels. If large groups of muscles participate in the work, on the other hand, the function of the heart and lungs determines the quantity of oxygen that can be supplied to the active muscles and thus the work they are able to perform. In exercise with a bicycle ergometer, for example, the magnitude of the active muscle mass does not under normal conditions seem to determine the oxygen uptake. It was found in some relatively young male subjects that the almost maximal oxygen uptake was practically the same whether the work was performed with only one leg or with both legs.[13]

In exercise continuing about three minutes with large muscle groups, such as bicycling or running, the magnitude of the work performed will depend on both the maximal oxygen uptake and the oxygen debt the individual can tolerate (FIG 1) If the oxygen uptake is determined just before the end of the work period, a maximal measure of the oxygen uptake and distribution (i.e, of the function of the circulation and lungs) during the form of work employed is obtained However, it should be emphasized that we do not obtain any absolute maximal value for oxygen uptake in this manner but rather a maximum for the type of work used

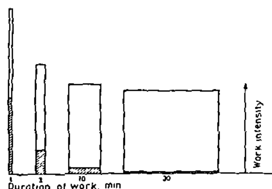


FIG 1 —The relation between aerobic and anaerobic (*shaded area*) work at maximal performance during periods of different lengths The calculations are approximate and are based on data from athletes Work of longer duration requires a circulatory and metabolic steady state when there is agreement between the oxygen uptake per unit of time and the work intensity. A measure of "maximal steady-state work" can be obtained from the work intensity or the oxygen uptake *per minute* during work of longer duration.

With more prolonged exercise only a decreasing proportion of the work can be performed anaerobically, and the total oxygen uptake becomes more and more dependent with increasing working time on the maximum oxygen volume that can be taken up during steady state between the demand and the distribution of the oxygen (FIG. 1).

The maximal steady-state value for oxygen uptake is influenced by the working time With 5 minutes' work the steady-state value for oxygen consumption is approximately 80 per cent of the oxygen consumption during exercise of short duration which produces total fatigue. In different individuals, however, the relation between the maximal steady-state oxygen uptake and the absolute maximal oxygen uptake differs. Very well trained athletes seem able to exploit almost the whole of the maximal oxygen uptake capacity during steady state

In very prolonged exercise, the mobilization of the energy reserve determines the magnitude of the work performed

From the foregoing it is evident that different measures can be used to gauge the *physical working capacity* depending on our definition of the term. Do we mean the ability to perform work of great magnitude during a brief or a long period? To take examples from sports, the question can be stated · Is it the 100, 1,500 or 10,000 meter runner's or the marathon runner's working capacity we wish to measure?

The capacity of performing work of considerable magnitude during a moderately long period should be a better expression of the physical fitness of an individual in the common meaning of this concept than the capacity to perform greater work during a very short or long time period As is evident from the foregoing, a measure of this can be obtained by *estimation of the upper limit of work during* steady state, either as a measure on an ergometer in kilogram-meters per minute (Kg M./min.) or as oxygen uptake per minute.

The measured value for maximal steady-state work is not absolute, however, because the body is quite unable to maintain circulatory and metabolic equilibrium over a protracted period The pulse rate rises even during slight

exercise if the work is continued a sufficiently long time. Even the most highly trained runner must adapt his speed to the distance he is to cover. However, we can speak of a relative steady-state value when the pulse rate, serving as an indicator of circulatory equilibrium, does not increase more than a certain number of beats in a specified time.

Blood Circulation During Work

The oxygen uptake during work does not normally seem to be limited by the respiration (see Chapter 41). This would seem to apply in any case for work up to the maximal steady-state level. In work with large muscle groups, accordingly, the oxygen uptake is determined by the blood circulation, i.e., by the cardiac output and the quantity of oxygen the blood can take up in the lungs.[15] This depends on the oxygen capacity of the blood and the quantity of oxygen which is given off in the periphery or, in other words, the oxygen saturation of the blood pumped by the right ventricle into the lungs. The unloading of the blood in the systemic circulation is determined by the efficiency of blood oxygen utilization in the working muscles and by the proportion of the cardiac output passing the working muscles, i.e., how effectively the blood is shunted to them.

Under normal conditions, the oxygen capacity of the blood varies relatively little in different individuals, and minor variations appear ordinarily to be compensated through variations in the utilization of the blood oxygen. Thus, the factors which determine the maximal steady-state work are cardiac output and the effectiveness of the adaptation of the peripheral circulation.

The cardiac output is determined by the stroke volume of the heart and the pulse rate. It was formerly believed that the stroke volume of the heart could vary to a great degree with the regulation of the circulation to meet varying demands. More recent investigations have altered this conception.[35, 39, 40] In man, and apparently also in dogs,[34] the stroke volume of the heart has been found to remain practically unchanged during work. In association with changes in the blood distribution, e.g., with changes in body position, the stroke volume can change under normal conditions, but in one and the same body position the stroke volume remains unchanged even up to pulse rates of 180 per minute, to judge from observations in the author's laboratory. Accordingly, the cardiac output increases during work entirely or almost entirely as a result of an increase in the pulse rate (Fig. 2A).

The pulse rate during work increases linearly with the magnitude of the work and the volume of oxygen taken up.[1, 5, 33, 42] The maximal pulse rate for a certain form of exercise, e.g., bicycling or running, varies comparatively little from individual to individual; in adults, the mean is about 195 beats per minute.[5] It is higher in children and probably lower in the elderly.[8, 33] The maximal steady-state pulse level is dependent on the duration of work and the degree of training of the individual. In younger, ordinary individuals the level is about 170 beats per minute. It is lower in completely untrained individuals and somewhat higher in the particularly well trained.

The oxygen saturation of the mixed venous blood decreases linearly, on the whole, with increases in the magnitude of the work performed and the oxygen uptake.[11, 33] The oxygen saturation of the venous blood from the working muscles falls exponentially toward a certain minimum[12] (Fig. 2B). The proportion of the cardiac output that passes through the working muscles increases, however, with the work load. The interference between these two functions will be largely a linear decrease in the oxygen saturation of the blood returning to the right heart. Since the oxygen saturation of the arterial blood remains largely unchanged during work, the arteriovenous oxygen difference will, for the most part, reflect the changes in the oxygen saturation of the mixed venous blood (Fig. 2B).

During work, the lactic acid concentration in the blood rises, but only slightly, at low work loads. The lactic acid concentration increases with the work load, and up to a certain work level the lactic acid concentration remains comparatively constant with an unchanged work load. During maximal work, continuing a few minutes, the lactic acid concentration rises rapidly and usually reaches maximal

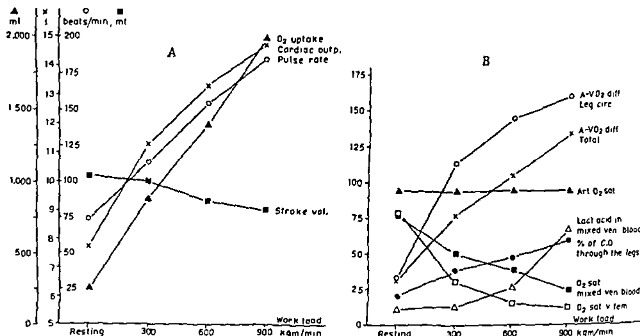


FIG 2 —The oxygen distribution during work The data were obtained at heart catheterization of a male experimental subject with normal circulation The ordinate in B shows (1) the percentage of the saturation value for oxygen in the blood, (2) milliliters of oxygen per 1,000 ml blood for the arteriovenous difference and (3) milligrams per 100 ml blood for lactic acid The decrease in the stroke volume at the higher work loads in this case can be explained by the fact that the numerous determinations required a large number of blood samples, thus decreasing the blood volume

studies during the first minutes after the exercise[1, 33] When different subjects are compared, widely varying lactic acid values are obtained for a certain work load, according to the physical working capacity of the individual and his physical training The relationship between the lactic acid concentration and the pulse rate in different normal subjects, however, is largely the same.[23] The lactic acid concentration increases more rapidly first when the pulse rate is above 160 In well trained athletes, on the other hand, the lactic acid concentration rises at appreciably higher pulse rates. If we select as a criterion of maximal steady-state work the highest work load at which the lactic acid concentration remains at a level or shows a moderate rise, it would seem to agree reasonably well, for individuals in ordinary physical condition, with the maximal work at which the pulse rate remains stable. In certain individuals, however, the pulse rate can increase rapidly with unchanged work load and without a particularly high lactic acid level It is therefore necessary to distinguish between a circulatory steady-state value, when the pulse rate is stable (and the stroke volume may be assumed to be unchanged), and a muscular steady-state value, when the lactic acid concentration attains a level In ordinary cases these two steady-state values lie at a pulse rate of about 170 (FIG 3)

From the foregoing discussion it is evident that an individual's capacity for physical work at steady-state is dependent on the following factors: (1) the stroke volume of the heart, which is largely constant at the same type of work, (2) the maximal pulse rate for work at steady-state, (3) the proportion of the cardiac output that is shunted to the working muscles; (4) the maximal blood-oxygen utilization in the working muscles at steady-state, and (5) the oxygen capacity of the blood.

The first of these functions is dependent on the size of the individual, whereas functions 2 to 5 vary independently of the size. Functions 1 and 2, and probably to a certain extent function 3, vary with the degree of training of the subject. Functions 4 and 5 vary under normal conditions relatively little and may compensate each other. Functions 1, 2 and 3, accordingly,

primarily determine the physical working capacity of the individual under these conditions.

An individual's maximal working capacity (i e., for work of short duration to total fatigue) depends on functions 1, 3 and 5 and also on the absolute maximal pulse rate during work, the absolute maximal oxygen utilization in the working muscles and the maximal oxygen debt that can be tolerated. The maximal oxygen uptake under these conditions is dependent on the same functions with the exception of the anaerobic working capacity. Consequently, it may be expected that a good correlation exists between the maximal oxygen uptake during work of brief duration and the work and oxygen uptake, respectively, during maximal steady-state work. Such has also proved to be the case in individuals of various ages.[1]

From these observations, the conclusion may be drawn that assessment of the aforementioned functions may be obtained from an individual's maximal steady-state working capacity (as well as the maximal oxygen uptake). For example, if the pulse rate is determined during work and the work is considered in relation to it (e g., at a pulse rate of 170), the work value serves as a direct measure of the stroke volume provided functions 3, 4 and 5 do not vary significantly between the individuals This may be assumed to be the case in normal individuals with ordinary physical training.

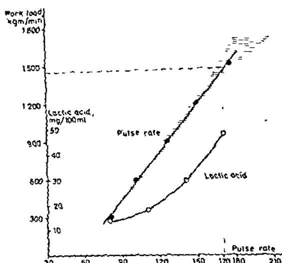


FIG 3 —Determination of the physical working capacity from the pulse-work ratio The pulse rate increases linearly with the load; the filled circles are obtained from an actual case The greatest deviations from a linear regression line are usually found at (a) low pulse rates depending on the degree of deviation of the subject from his basal metabolic state before work and (b) at pulse rates above 170 when there is usually not a steady state The regression line and by extrapolation the value for work at a pulse rate of 170 are determined from the pulse rate after six minutes' work under different work loads with a maximum pulse rate of 160 and 170 beats per minute If there is not a circulatory steady state at the highest load, i e, if the pulse difference between the second and the sixth minute exceeds 10 beats, the work value is usually reduced to the value at pulse 160 or possibly a lower value, depending on the pulse level and the pulse rate increase under a constant load. The lactic acid curve constitutes the mean curve for normal subjects [22]

Physical Working Capacity in Normal Subjects

A relative measure of the physical working capacity can be obtained in different ways, as is evident from the foregoing. The maximal work performed by an individual during a period of several minutes can be measured on an ergometer of some type. If the work requires participation of large groups of muscles, this measure gives a value for the sum of the maximal aerobic and anaerobic working capacities. If the oxygen uptake is determined at the end of such a maximal work performance, a measure of the maximal aerobic working capacity is obtained[1, 4] Thus, it is a maximal measure of the adaptation of the lungs and the circulation during work of a particular type.

A conception of an individual's capacity for work continued over a longer period is obtained from the individual's maximal steady-state work. A measure of this is obtained by having the subject perform work under different loads and by determining the pulse-work ratio. In subjects in a state of ordinary physical training, the pulse rate of 170 comprises, on the average, the upper limit for a relatively steady state; the work performed at this pulse level can be determined directly or by extrapolation from the pulse-work ratio (FIG 3). If the pulse rate does not attain a level at the top load, the work performed at a lower pulse rate is given as the maximal steady-state work, e g., at a pulse rate of 160. Determination of the maximal steady-state work in this manner naturally

involves approximation. The error in judgement under ordinary conditions, however, will not be as large as might be anticipated If, for example, the maximal steady-state pulse rate in an individual is 180 instead of 170, the error introduced into the computation of the working capacity will be below 10 per cent, which is a small error in comparison with the large individual variations.

The pulse-work ratio for loads under the upper steady-state level gives in itself a measure of the capacity of the circulation during work and can be used as a relative measure of the working capacity However, inasmuch as different individuals can have varying maximal steady-state pulse rates, the pulse-work ratio for submaximal work gives only a rough estimate of the individual's working capacity during a longer period of exercise

In the selection of a method for determination of the physical working capacity, it must be kept in mind that determination of the maximal work performance or the oxygen uptake during short work periods requires that the subjects be in training for exercise and willing to subject themselves to the exertion. As a rule, an effort should also be made by determination of the lactic acid concentration at the end of the exercise to establish that the work actually was maximal Determination of the pulse-work ratio or the oxygen uptake in the case of a submaximal work load or maximal steady-state work demands considerably less cooperation from the subject and is therefore easier to carry out. If the work is performed on a bicycle ergometer, the work that can be estimated from the setting of the ergometer, and the pedaling rate can be used as a relative measure of the energy output since the mechanical efficiency of bicycling does not vary to a great degree from subject to subject [1, 42] Even well trained racing bicyclists have proved to have the same efficiency as ordinarily trained subjects.[16] This greatly simplifies the determination.

As pointed out earlier, the correlation is rather high between the work-pulse ratio or the maximal steady-state work and the maximal oxygen uptake in exercise of short duration and of the same type. Therefore, the pulse-work ratio has been used with submaximal work on the bicycle ergometer for indirect estimation of the maximal oxygen uptake.[2] A nomogram has been constructed for such a determination There is usually nothing to be gained by expressing the working capacity in terms other than those directly determined, except possibly to create the impression that the examination was more complicated than was actually the case. Computation with the aid of the nomogram also involves an unjustified approximation, since it assumes that the maximal pulse rate is the same in different individuals Of course, the procedure does not allow determination of the maximal working capacity or the oxygen uptake with greater accuracy than if the work or the oxygen consumption at a certain pulse rate is used. Nor does it take into consideration that the maximal steady-state level varies in different individuals.

The writer has for several years used determination of the pulse-work ratio and the maximal steady-state on a bicycle ergometer to obtain a relative measure of the capacity for physical exercise [36, 42] Usually, work loads of 200, 400 and 600 Kg M. per minute are used for women and of 300, 600 and 900 Kg M. per minute and possibly higher for men. The exercise is performed for periods of six minutes with each load, and, as a rule, the largest load produces a pulse rate which approximates 170 per minute If a relatively steady-state (variation of the pulse rate between the second and the sixth minute by not more than 10 beats per minute) existed up to that level, the work at a pulse rate of 170 was determined by extrapolation. If a steady-state with respect to pulse rate was not attained at the top load, the work at a rate usually of 160 beats or the highest steady-state work was reported.

The method has proved of practical value in different applications such as in assessment of the condition of athletes, in placement of workers in suitable occupations and in studies of the effects of physical training (Fig. 4) on different groups such as athletes and military conscripts.

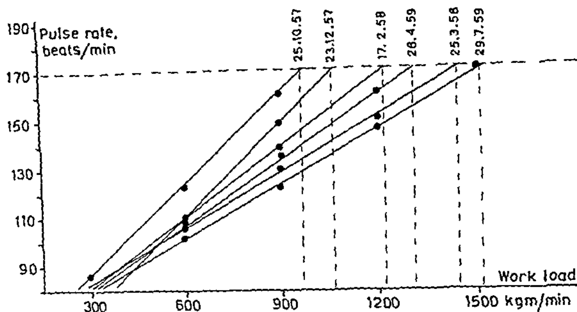


FIG 4 —The effect of physical training on the pulse-work ratio in the same experimental subject The training was carried out at varying intensity during the period from October 1957 to July 1959 Before the training, the test subject was unable to perform 1,200 Kg M per minute for more than one minute, in July 1959 1,800 Kg M per minute was possible for two minutes Paralleling this increase, the pulse rate decreased at each work load and the estimated steady-state work varied from 1,000 to 1,500 Kg M per minute

Bodily Measurements of Physical Working Capacity

The capacity for physical work varies with sex, body size, constitution and physical training. The working capacity in proportion to size is lower on the average in women than in men The variations with degree of training and physical constitution in both sexes are extremely wide, it is, therefore, impossible to estimate, with any degree of accuracy, the physical working capacity in adults from a measurement of the body size Consequently, it has been necessary to relate other parameters to the physical working capacity. This has been of interest, for example, in evaluating the fitness of an individual for heavy physical work during military service[30] or in occupations requiring heavy manual labor. By comparing the directly determined physical working capacity with a predicted value, it should also be possible to establish the existence of impairment of the normal adaptation of the blood circulation and respiratory function during work.

It has been demonstrated that there is a direct correlation between the physical working capacity determined by the pulse-work ratio or as the maximal steady-state work, and the total amount of hemoglobin and blood volume of the body[24] The same applies, as might be expected, to the maximal oxygen uptake during work of brief duration.[3] It has also been shown for the maximal steady-state work determined from the pulse-work ratio that there is a linear correlation with the heart volume as determined by means of roentgen examination of the chest The exposure is made at the end of diastole with the subject in the prone position.[25, 26] The relation between these measurements is the same in small and large subjects, children and adults, men and women, the physically well trained and the untrained. Thus, it is possible with a standard error of estimate of approximately 10 per cent to assess the physical working capacity of an individual from both the blood volume, or the total amount of hemoglobin, and the heart volume. Consequently, in evaluating a large population, the individuals with especially poor qualifications for physical work can be "weeded out" and those par-

ticularly well adapted for such activity can be selected.

The relation between the heart volume and the blood volume on the one hand and the physical working capacity on the other may be explained by the fact *that there is a variation* between different individuals in the pulse-work ratio, primarily with the stroke volume of the heart, *as has been related above Among* the other variables that determine the physical working capacity the adaptation of the peripheral circulation varies independently of the body size, sex (on the whole) and, in an ordinary population sample, of the degree of physical training. This also applies in part to the oxygen capacity of the blood The stroke volume of the heart during work, which, as pointed out earlier, is the same as at rest, is determined by the diastolic filling volume of the heart, which is also the same at rest and during work up to a pulse rate of about 150 The diastolic filling volume of the heart depends in turn on the pressures in the central vessels, which are functions of the total blood volume [37]

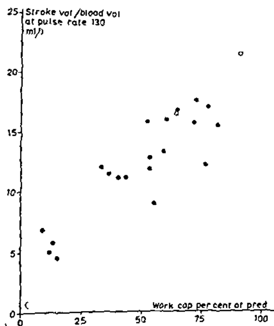


Fig 5.—The ratio of stroke volume to blood volume during work at a pulse rate of *130 is plotted on* the ordinate against the work capacity on the abscissa

dominant mitral stenosis, open circles denote [illegible] dominant regurgitation

Clinical Application of Work Tests

Pathophysiologic Background

Under pathologic conditions, the physical working capacity can be reduced, either because *the functions that normally determine* the working capacity are changed, or because other functions that do not normally limit the working capacity determine the maximal work that can be performed

Under normal conditions, the capacity to perform work at steady-state is limited, as shown earlier, by the stroke volume of the heart and the adaptation of the peripheral circulation. Different kinds of heart disease, both acquired and congenital, can influence the effective stroke volume of the heart. In valvular defects with regurgitation, stenosis or shunting of the blood between the left and right heart or the great vessels near the heart, the effective stroke volume of the heart, i e, that part supplying the systemic circulation, can be greatly dedecreased In these cases, the physical working capacity, as is to be expected, is reduced (Fig 5)

In slight to moderate valvular defects, however, the effective stroke volume may be of normal magnitude due to compensation of the impairment In regurgitation and shunting, this takes place through enlargement of the heart chamber where the function is affected by the lesion, with the result that it pumps a greater stroke volume than the other ventricle so that the regurgitated, or respectively shunted blood volume, is added to the effective stroke volume. For example, in cases of atrial septal *defect*, the right ventricle can pump three times the stroke volume of the left ventricle. In stenosis, the obstruction is compensated *by a rise* in pressure (e g., in mitral stenosis in the left atrium and pulmonary veins), or by increased work *performed by the ventricles* (*e g*, by the left ventricle in aortic stenosis). In cases of slight valvular defects, the impairment is usually *completely compensated* in this manner. Physical training can result in still more effective compensatory adaptation, and even high-grade valvular defects can be compensated so that the patient has a capacity for physical work greater than the average for normal un-

trained subjects. In this compensation, the affected part of the heart is predominantly enlarged and consequently the heart as a whole. Thus, the physical working capacity becomes less than normal in proportion to the heart volume. On the other hand, with full compensation the working capacity is usually in relation to the blood volume.

In cases of very pronounced decrease in the effective stroke volume of the heart with reduced cardiac output at rest and practically no increase in the cardiac output during work, the oxygen uptake can increase during work because the blood is directed to the working muscles to a greater extent than during rest and because the blood is unloaded to a very full extent in the musculature. In these cases, the physical working capacity is very low. In slight to moderate valvular lesions, the impairment is not compensated or only partially compensated in this manner.[10, 11] The relationship between the decrease in physical working capacity and some hemodynamic data in cases of mitral stenosis, is demonstrated in FIGURE 6.

Impairment of the peripheral adaptation of the circulation with resulting low physical

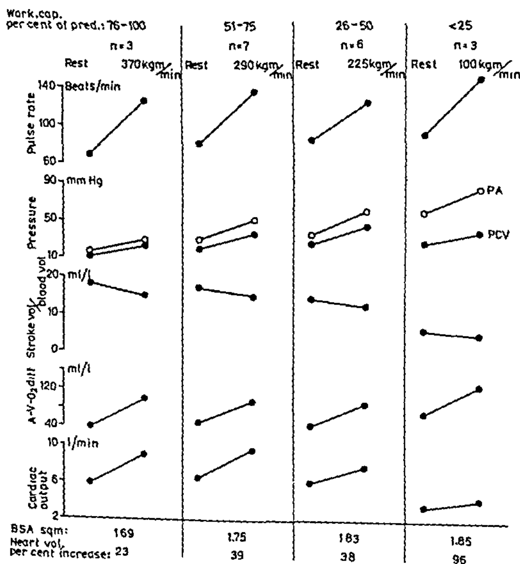


FIG. 6.—The relation between the decrease in physical working capacity (in percentage of predicted value) and certain hemodynamic data in cases of isolated mitral stenosis. PA = pulmonary artery, PCV = pulmonary capillary-venous pressure (pulmonary artery wedge pressure), n = number of subjects in group.

ticularly well adapted for such activity can be selected.

The relation between the heart volume and the blood volume on the one hand and the physical working capacity on the other may be explained by the fact that there is a variation between different individuals in the pulse-work ratio, primarily with the stroke volume of the heart, as has been related above. Among the other variables that determine the physical working capacity the adaptation of the peripheral circulation varies independently of the body size, sex (on the whole) and, in an ordinary population sample, of the degree of physical training. This also applies in part to the oxygen capacity of the blood. The stroke volume of the heart during work, which, as pointed out earlier, is the same as at rest, is determined by the diastolic filling volume of the heart, which is also the same at rest and during work up to a pulse rate of about 150. The diastolic filling volume of the heart depends in turn on the pressures in the central vessels, which are functions of the total blood volume.[37]

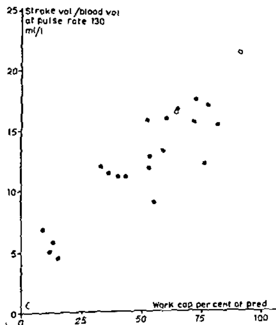


FIG. 5.—The ratio of stroke volume to blood vol-

dominant mitral stenosis, open circles denote isolated

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out or must be possible to perform when needed in conjunction with the work tests for a more comprehensive clinical evaluation:

1. Pulse rate counting during work for determination of the pulse-work ratio.
2. Respiratory rate counting, possibly determination of ventilation and oxygen consumption, also, in analysis of the respiratory functions and to provide a measure of the work load.
3. Recording of the electrocardiogram during and after work
4. *Determination* of the arterial oxygen saturation during work with an oximeter or by means of an arterial catheter.
5. Determination of the lactic acid concentration in blood from the larger central vessels or in *finger* blood samples
6. Determination of the total blood volume or total amount of hemoglobin.
7. Roentgenologic estimation of the heart volume, with the patient in the prone position and with exposure at the end of *diastole*.[24]

Of these investigations, 1, 2 and 3 should always be performed, 6 and 7 when no very pronounced heart disease is present, 4 when the case gives reason to assume the existence of a right to left shunt and 5 when there is a suspicion that peripheral vascular changes are present.

The requirements set up for a clinical work-testing procedure limit to a great degree the selection of a type of work. If it is planned to follow the pulse, respiration, arterial oxygen saturation, blood lactic acid concentration and to record the electrocardiogram while work is being performed, the patient must remain *stationary*. A *suitable form* of work is exercise on a bicycle ergometer, which also has the advantage mentioned earlier, i e., that the work value setting on the ergometer can be used as a relative measure of the energy expenditure. For more exact determination, especially in older subjects who are wholly unaccustomed to bicycle exercise, it *may* also be expedient to determine the oxygen uptake Naturally, for more limited examinations other forms of work can be employed, e g., running or walking on a treadmill, running up stairs or stepping up and down from a bench The work load in these tests must be graded through determination of the oxygen uptake. In *these work tests*, however, it is impossible as a rule to record the electrocardiogram during the exercise, which should be an absolute prerequisite considering both the diagnostic value of the electrocardiographic data and the risk to the patient if it is omitted.

When a bicycle ergometer is used, about 60 per minute is a suitable rate of pedaling. It is preferable that the ergometer be designed so that the load is automatically corrected with variation of the rate of pedaling.[22] It should also be possible to use the bicycle ergometer for work in both sitting and reclining position

The pulse rate and the respiratory rate are most easily determined by auscultation. The electrocardiogram should preferably be recorded during the work with a direct-writing apparatus The electrocardiogram provides a check on the pulse rate, and the ECG pulse value may replace the auscultatory if desired. During the work, naturally only chest leads can be used The indifferent electrode should be placed on the forehead and the other electrodes at positions 2, 4 and 7, as well as possibly 1 and 3. The electrocardiogram should be recorded repeatedly and at each load so that the test can be interrupted quickly if electrocardiographic changes of coronary insufficiency type appear. When shunting of blood from the right to the left heart or respiratory impairment is suspected, oximetry with an ear oximeter should be done If more detailed analysis is planned, such as determination of carbon dioxide tension (as in cases of suspected respiratory impairment), an arterial needle or catheter is inserted.[3] The arterial blood pressure during work may also be measured using the same arterial needle or catheter. The arterial blood pressure is particularly of interest when hypertension is suspected. If it is desired to measure serially the lactic acid concentration in the blood, it is usually adequate to collect blood samples from the warmed fingertip The blood is allowed to drop onto a watch glass.

Evaluation of the physical working capacity under pathologic conditions

The work or the oxygen uptake at a pulse rate of 170 estimated from the pulse-work ratio, possibly with correction downward when a steady-state is not achieved, can only be used as a measure of the physical working capacity of an individual when the circulatory adapta-

working capacity has recently been described.[17] The pathophysiologic syndrome has been termed "vasoregulatory asthenia" The impairment is characterized by normal cardiac function but decreased utilization of the blood's oxygen, so that the oxygen content of the mixed venous blood is high, usually during both rest and work It has been demonstrated that this is caused by a disorder of vasoregulation, resulting in a smaller than normal increase of the blood flow through the working muscles in relation to cardiac output A certain degree of vasoregulatory asthenia may occur in otherwise completely asymptomatic patients with low working capacity Even in cases of slight cardiac disease the peripheral circulatory adaptation during work may be less effective than normal. This, together with other changes, can contribute to a lower than normal physical working capacity.

The physical working capacity can also be decreased because of reduced oxygen content in the blood such as in anemia and impaired pulmonary function (see Chapter 41)

Under pathologic conditions, the working capacity can be limited by the oxygen supply to the heart muscle itself. The stroke volume of the heart, as well as the adaptation of the peripheral circulation, can be normal in these cases, but under a certain work load, symptoms of coronary insufficiency may appear (angina pectoris and S-T-T changes in the electrocardiogram) The work cannot usually be made to exceed this limit even if only a minor part of the central circulatory capacity is used.

In patients with congenital heart disease and shunting of the blood between the right and left heart the cardiac output can increase, but the arterial oxygen saturation falls to such a great extent that the anoxia, particularly in the central nervous system, prohibits a further increase in the work load.

The working capacity can also be limited by the muscularity itself. In older, completely untrained patients, with arteriosclerotic vascular changes or neuromuscular disturbances, the musculature can limit the work so that the central circulatory adaptation does not reach a maximum. In these cases, the patient cannot force his work performance up to a higher pulse rate than normal. Such may be the case, but often in these instances the limitation of the working capacity is muscular rather than circulatory. In cases of localized peripheral vascular changes, the work is inhibited by pains from one or both legs, and the blood lactic acid concentration rises rapidly even at a low pulse rate.[9]

A number of different disturbances of cardiac function can occur during work and may induce subjective symptoms without, however, limiting the working capacity. Extrasystoles, paroxysmal tachycardia or paroxysmal atrial fibrillation may occur at a certain work load The patient feels discomfort, and the heart beats irregularly and hard. At examination during rest and after exercise the condition may be completely normal, only during work, often only under a heavy work load, do manifestations appear which are revealed primarily by the electrocardiogram

Tests of Physical Working Capacity

From the foregoing discussion of the pathophysiologic background, it is evident that a clinical determination of the physical working capacity must demand considerably more extensive investigations than work tests applied to normal individuals require In clinical testing it is not sufficient to obtain a certain measure of the maximal steady-state work or the maximal oxygen uptake To permit a correct evaluation of the work test a conception must also be obtained of (1) the relation between the working capacity and the circulatory conditions, correlation with the heart volume and blood volume, (2) the function that limits the working capacity, i e , the central circulation, the pulmonary function, the blood flow through the coronary vessels, shunting of blood between the right and left heart, the adaptation of the peripheral circulation and the musculature; and (3) evidence of impairment of cardiac function, such as arrhythmias and conduction disturbances For this, it is necessary that the work testing as a link in the chain of cardiac diagnoses includes analysis of a number of functions and that the results be correlated with morphologic measurements of the circulatory system.

mal in relation to the blood volume, as, e.g., when compensation of the valvular defect or anomaly is complete But in such instances it may be very low in proportion to the heart volume, if the compensation has required an appreciable enlargement of the heart (FIGS. 8 AND 9)

Physical training can greatly increase the working capacity, even in patients with valvular defects, as mentioned earlier. In these patients, the working capacity can be average or almost average in relation to the blood volume while it is low in relation to the heart volume. The increase in the working capacity is paralleled, in these patients, as in normal subjects, by an increase in the dimensions of the vascular system, but the relation between the heart volume and the blood volume will be other than in normal individuals[20, 39] The importance of correlating the physical working capacity with the blood volume and heart volume in clinical evaluation should be apparent from these observations.

In patients with so-called vasoregulatory asthenia, the aforementioned impairment in the adaptation of the peripheral circulation, the physical working capacity is low—and can be extremely low—in relation to the heart volume and blood volume, while the relation between these latter two values is normal (FIG 10). These cases are variously diagnosed as cardiac neurosis, neurocirculatory asthenia, organic valvular defect, coronary disease, myocarditis or residual symptoms following myocarditis.[17] It has therefore proved to be of great importance in the classification of cardiac patients to separate patients with vasoregulatory asthenia, who can have pronounced subjective heart symptoms but who have normal cardiac function. It has also proved possible through physical training to restore completely the physical working capacity and even to exert considerable influence on the subjective symptoms in patients with vasoregulatory asthenia.[19] As a result, the relation between the working capacity and the heart volume or, respectively,

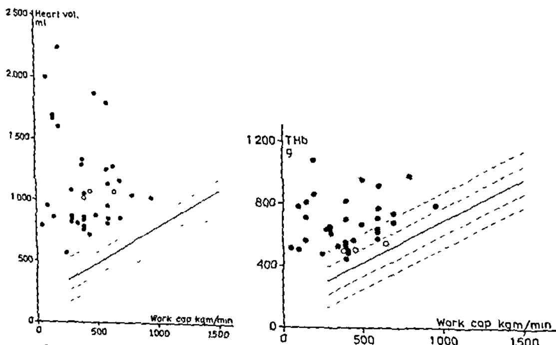


FIG 8.—Th... amount of h... line represe... jects.[18] The dotted li... note isolated or pred... gurgitation. Note th... which fall within the normal distribution when physical working capacity is correlated with total hemoglobin (i e., well compensated cases) fall outside the field of normal distribution when correlated with the heart volume

tion is the limiting factor. If symptoms of coronary insufficiency appear at a lower work load or there is pronounced dyspnea, as with increased pressure in the pulmonary circulation, the measurements obtained cannot be used for this purpose Even in these cases, however, the pulse-work ratio provides a certain understanding of the circulatory adaptation, i e , of the stroke volume of the heart and the responsiveness of the peripheral circulation. This has been demonstrated in investigations with heart catheterization (FIG 5) Accordingly, in such cases a distinction should be made between the work-test as a procedure, which permits an understanding of circulatory adaptation during work, and a technic used to assess the fitness of a patient for physical work or a certain occupation. The latter assumes that other limiting factors are taken into consideration

If there are no signs that factors other than those normally limiting the physical working capacity constitute an obstacle to work approaching the upper steady-state value, the evaluation of the working capacity can be carried out in the same manner in patients with heart disease as in normal subjects In severe cases, it is frequently impossible to reach pulse equilibrium even with very small work loads In these cases, however, the work test is of little interest other than to establish that the working capacity is very low. In patients with atrial fibrillation the same evaluation can usually be carried out as in cases of sinus rhythm (FIG 7). There are fibrillation cases, however, in which high ventricular frequencies are quickly reached and in which assessment may prove exceedingly difficult On the other hand, the work-test is of negligible importance in these cases, too, as the working capacity is very low.

As pointed out earlier, the capacity for physical work does not afford a direct assessment of the severity of the pathologic lesion as it can be compensated to some extent. However, if the work value is correlated with the roentgenologically measured heart volume, a better idea of the severity is obtained Patients with valvular defects or anomalies of different kinds almost always have a low working capacity in relation to heart volume. The effectiveness of the compensation can be gauged if the working capacity is correlated with the blood volume or the total amount of hemoglobin The working capacity can be quite nor-

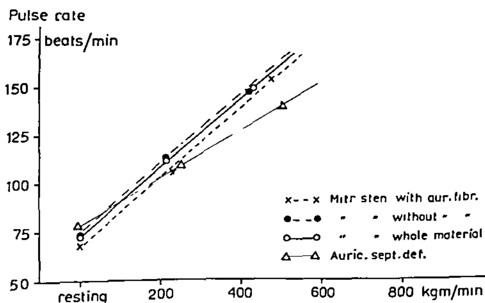


FIG 7 —Pulse-work ratio in groups of patients with mitral stenosis—some with atrial fi- ... The ... teno- ... dur-

ing work in cases of atrial septal defect but remains unchanged or decreases in the ca es of

the blood volume becomes normalized. The increase *in the working capacity* takes place, *accordingly*, through a regression of the circulatory impairment and not, as in patients with valvular defects, through enlargement of *the heart* Determination of the physical working capacity, the blood volume and the heart volume has made it possible to demonstrate this functional impairment and to find therapeutic measures to cure it, returning formerly wholly incapacitated patients to full working capacity.

Evaluation of the Electrocardiogram During and After Work

The recording of the electrocardiogram should always be a part of a clinical work-test The *electrocardiogram should* be *recorded* as well during as after the work,[43] preferably with a direct-writing apparatus so the record can be observed during the test. In many cases, a marked S-T depression of the coronary insufficiency type appears before any subjective symptoms are manifest. In other cases, ECG changes appear simultaneously with characteristic symptoms of angina pectoris The ECG change is usually accentuated after the work and is especially pronounced after two to five minutes. The ECG change may persist half an hour or longer. The patient should rest as long as the ECG change is evident. In the case of severe angina pectoris pains, the patient obtains relief from breathing oxygen for a few minutes or from nitrite preparations Therefore, these should always be available. If the work test is interrupted immediately after the appearance of subjective or objective signs of coronary insufficiency, the ECG changes may quickly subside and are then most clearly *evident during* or immediately after the work.

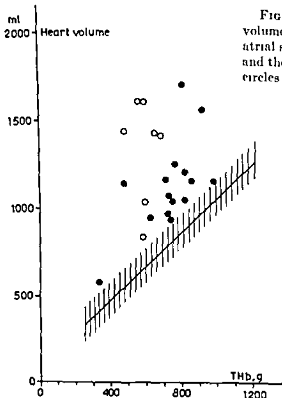
The interpretation of the ECG changes of coronary insufficiency type during and after work demands experience in electrocardiographic diagnosis The *placing of the indifferent* electrode on the forehead during the work does not notably change the criteria for a pathologic electrocardiogram. A marked depression of the whole S-T segment and the appearance of *negative to* diphasic T waves in the extremity leads and chest leads 4 to 7 are usually considered definite signs of coronary insufficiency. Such phenomena are not always present. Patients with marked sympatheticotonic reactions, especially in cases of the previously mentioned vasoregulatory asthenia, may present the same picture.[21] It is manifested in these cases primarily during work and subsides after the work parallel with the pulse rate. ECG changes of the same type, and often even more pronounced, appear when these patients are in the upright position (FIG 11). It is, therefore, often of great value to combine the work testing in these cases with orthostatic tests, such as standing for eight minutes while the electrocardiogram is recorded. In true coronary disease S-T-T changes very seldom occur in the upright position if the resting electrocardiogram is normal

Another cause of S-T changes during work is chronic myocarditis[4, 6] Here, too, the changes are usually more definite in the upright position and subside along with the pulse rate after work. Another common source of error, which is most *often overlooked*, is *so-called pre-excitation* occurring with Wolff-Parkinson-White syndrome. This is usually seen at rest but in some cases may appear only during work and *disappear rapidly on cessation of activity*. In conjunction with the occurrence of the delta wave (preexcitation), the S-T segment is depressed.

Finally, it should be kept in mind that digitalis causes an S-T depression which is accentuated *during and after work*. *Even several* weeks after discontinuance of the digitalis and after the resting electrocardiogram has become entirely normal, marked S-T-T depressions may occur in connection with exercise.

In addition to S-T-T changes, a number of different disturbances may be seen in the electrocardiogram during and after work. Extrasystoles, both supraventricular and ventricular, paroxysmal tachycardia, periods of atrial flutter and fibrillation, all may occur These disturbances may be signs of coronary insufficiency, myocarditis or valvular defects with myocardial involvement. In other cases, the cause is more difficult to establish, but the observation can contribute to explaining *the* subjective symptoms of the patient, e.g , palpitation and irregular rhythm on exertion.

If extrasystoles and arrhythmias increase



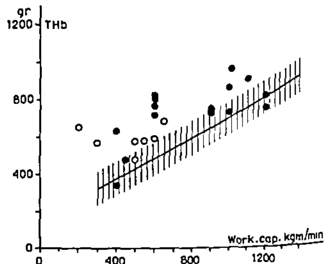
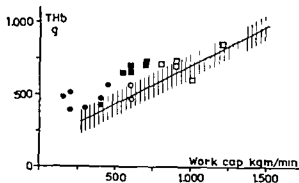


FIG 9—The physical working capacity in relation to the heart volume (*left*) and the total amount of hemoglobin (*right*) in cases of atrial septal defect [24] The straight line is the normal regression line and the shaded area shows ± the standard error of estimate. Filled circles represent males and open circles females



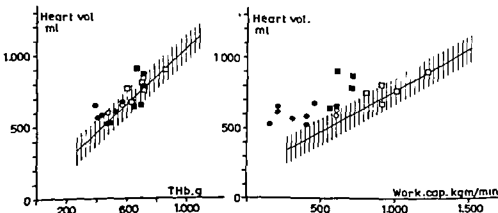


FIG 10—The physical working capacity in relation to the total amount of hemoglobin (*above*), the heart volume (*right*) and the heart volume in relation to the total hemoglobin (*left*) in cases of vasoregulatory asthenia and in some healthy individuals (open symbols) Straight lines and shaded area are as in FIGURE 9 Squares denote males, circles females Pa- ... low physical working capacity in re-

pulse reactions, however, the difference may be great. The functional work capacity determined from testing in sitting position in these cases can be lower than normal in relation to the heart volume and blood volume. This can be interpreted as a sign of impaired cardiac function The functional work capacity determined in recumbent position may be normal, suggesting that the cause of the low functional work capacity is probably to be sought in an unfavorable blood distribution, possibly due to a small blood volume in relation to the body height or to low venous tone. In patients with valvular defects and pulmonary hypertension, on the other hand, the pulse rate under different work loads is frequently higher in recumbent than in sitting position. Signs of pulmonary edema can also appear in these patients during work in a reclining position. During work in a sitting position, it is my experience that pulmonary edema does not occur with the testing technic described here.[18] This observation can serve as a guide in diagnosis.

It is also important in routine heart catheterization to analyze the hemodynamics during work It is expedient to do this according to the same system with increasing work loads as in ordinary work testing In order to be able to adapt the work so that values for at least two loads can be obtained, the patient's working capacity should be tested in recumbent position a day or two before the catheterization It should be kept in mind that the pulse rate under a particular work load is usually somewhat higher in conjunction with heart catheterization

Work-tests in patients with atherosclerosis obliterans can be arranged on a bicycle ergometer by, for example, having the patient exercise one leg at a time.[9] Blood samples can be obtained from the femoral veins, after introduction of a catheter, for comparison of the oxygen saturation and lactic acid concentration. For this purpose, it can also be sufficient to determine the lactic acid concentration in finger blood samples, as mentioned earlier, and then to correlate these values with the work load and the pulse rate. This gives a conception of the degree of severity of the impairment.

Work testing according to the system described here can also be arranged for arm exercise in evaluating the working capacity of the handicapped, e.g. in cases of leg amputation or paresis.

Risks Involved in Clinical Work Testing

Naturally, there are certain risks involved in exposing sick patients to bodily exertion in conjunction with work-tests. This applies principally to cases of coronary disease and acute myocarditis, but also to valvular defects, especially aortic. Sudden death may occur in these cases in direct connection with the work. To decrease the risks the following precautions should be observed:

1. Resting electrocardiogram should be recorded immediately before the work-test and should be examined by a physician On the slightest suspicion of an active myocardial change the test should be postponed until the change has proved to be stationary or has regressed

2 When there is reason to assume that an increased risk might be involved, the test should be started with a small load, corresponding approximately to walking on the level, 100 to 200 Kg M. per minute The work should be increased only if the patient experiences no subjective discomfort and if no electrocardiographic changes are found.

3. The personnel carrying out the tests should be thoroughly instructed and should recognize the most important electrocardiographic changes. A physician should be available if the patient's condition deteriorates during or after the test.

4. The patient should remain in a reclining position at least 15 minutes after the completion of the test, and the electrocardiogram should have returned to the resting status before the patient is permitted to get up The patient should not be exposed to rapid chilling, such as a cold shower, immediately after the test

If these precautionary measures are observed, the risk in testing the working capacity of even gravely ill patients is very slight My experience with clinical work-testing covers a period of 18 years and includes tests on about 20,000 subjects. During this time, sudden death occurred in one case in which the patient had been permitted to shower after the test. In another case in which the electrocardiogram had not been adequately analyzed before the test, a myocardial infarction was provoked or aggravated by the test.

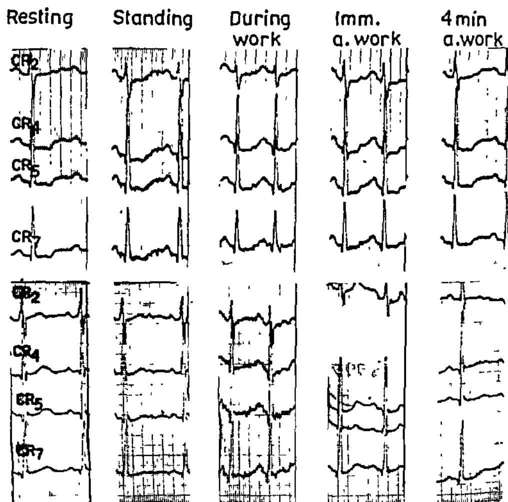


FIG 11 —Electrocardiogram (chest leads) from a patient with vasoregulatory asthenia at rest, upright position, during and after work The upper tracing was recorded before a period of physical training, the lower *after training at which time the circulation was completely* normal The work load before training was 100 Kg M per minute, after 400 Kg M per minute

during work, it should as a rule be regarded as a sign of organic heart disease; if, conversely, they *decrease* or *disappear* during work, the disorder is usually of less significance.[31]

In rare cases, first degree A-V block may occur during work More commonly there is prolongation of the conduction time at rest which disappears during work as the pulse rate increases This is important for evaluation of the *functional* significance of the disturbance If the conduction delay is maintained or prolonged during exercise, it follows that at a certain heart rate the atrial systole will occur during ventricular systole, the disturbance will counteract a rapid *filling of the* ventricles Intraventricular conduction block, of either the right or left bundle branch, may occur

changes Signs of right ventricular strain may appear in patients with pulmonary hypertension *Observations of this type in* patients with completely normal resting electrocardiogram may be of great diagnostic importance in many cases

Special Clinical Work Tests

As a rule, it is most expedient to carry out the work-tests with the subject in sitting or upright position Valuable information can be obtained, however, in work-tests in both sitting and recumbent positions In normal subjects the pulse-work ratio is either the same in these two positions or the pulse rate is somewhat lower or higher when work is performed in the recumbent position under the same loads In certain patients with pronounced orthostatic

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Summary

Work-tests can contribute extremely valuable information for the evaluation of the physical working capacity of patients with definite or suspected cardiac disease A number of diagnostically valuable data can be obtained during and after exercise The work-tests also provide a means for following the course of the disease and the effect of surgical or other therapy

In the present survey, I have not evaluated all the suggested methods of work-testing proposed in the literature. The majority of these do not meet the requirements which should be established for a clinical work-test Determination of one or two functions is not sufficient, since the factors which limit the physical working capacity vary in different pathologic conditions Methods making possible observations only after the completion of work are not satisfactory both because it is usually impossible after the work to establish which function limits the working capacity and because certain pathologic symptoms appear only or mainly during the work. Forms of work which do not permit measurement during a relatively steady state are also unsatisfactory. Such a steady-state is usually necessary for adequate precision in measuring such functions as oxygen consumption and the cardiac output

The physical working capacity preferably should be defined as the greatest amount of work (or the greatest oxygen uptake) which can be performed with large muscle groups under relative circulatory equilibrium This value corresponds better to the needs for a work-test which can be practically applied than the determination of maximal working capacity or oxygen uptake during brief periods of severe work which leads to complete exhaustion. These steady-state tests also involve less risk for the patient

A simple procedure is described which uses a bicycle ergometer or a similar stationary procedure for analysis of several circulatory functions during work. This technic permits determination of the specific function which limits working capacity as well as a measure of the maximal steady-state work. If the test is carried out with observation of certain precautionary measures, the risk to which the patient is exposed is negligible

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Section III

PHYSIOLOGIC ASPECTS OF CARDIOVASCULAR DISEASES

ing a congenital cardiovascular disorder are usually quite clear when each is studied systematically, the unraveling and understanding of problems presented by a particular patient may be quite complex; indeed, the natural history of the disease is most important. The complexity arises in considerable part because of the frequent coexistence of different kinds and combinations of abnormal circulatory loads, in contrast to the situation usually encountered in a patient with acquired heart disease where one abnormality or load is responsible for the clinical syndrome In a study of a patient with congenital heart disease one may be confronted, for example, with the task of assessing the combined effects of the pressure work load of pulmonic stenosis and the volume work load of an intracardiac shunt on the ventricles together with the physiologic aberrations produced by chronic arterial hypoxemia In the present section, we shall attempt to describe first what each of the various congenital abnormalities represents in terms of an abnormal load on the circulation and, second, to discuss the clinical evidences of these physiologic loads We should like to emphasize that in this section we are concerned with the specific anatomy of congenital abnormalities only in so far as it affects the hemodynamic consequences of a lesion, e.g., whether or not the aorta is dextropositioned in a patient with a high ventricular septal defect is not at present pertinent.

The various lesions are diagrammed in Figure 1 and tabulated in Figure 2 In group I (Figs 1 and 2,*I*) are the stenoses and obstructions which may occur congenitally in the circulation and impose a pressure work load on the ventricle upstream from the lesion. These disorders included valvular and infundibular pulmonic stenosis (*I-1*), pulmonary hypertension (*I-2*), coarctation of the aorta (*I-3*) and aortic stenosis (*I-4*) The second category of abnormalities (Figs 1 and 2,*II*) includes those which, because of abnormal intravascular communications, result in increased volume work loads In each of these lesions one or both of the ventricles are required to eject an abnormally increased stroke volume. In ventricular septal defect (*II-1*) the left ventricle pumps blood not only through the aortic valve but also into the right ventricle. The right ventricle ejects not only the blood which has flowed into it during diastole from the right atrium but also the increased amount of blood which enters it from the left ventricle during systole In the presence of an atrial septal defect (*II-2*) or aberrant pulmonary veins (*II-3*), the right ventricle ejects an increased amount of blood which has flowed into it during diastole. In patent ductus arteriosus (*II-4*), the left ventricle ejects the increased amount of blood which bypasses the systemic circulation through the ductus to the pulmonary artery and thence back to the left atrium. In mitral (*II-5*) and tricuspid (*II-7*) regurgitation the downstream ventricle ejects blood not only into its arterial outflow but also back through its regurgitant atrioventricular valve. Aortic regurgitation (*II-6*) presents a similar load

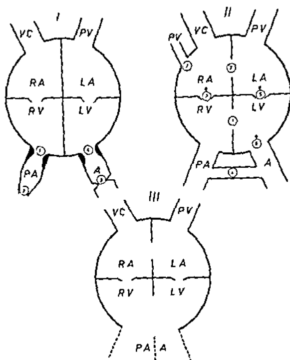


Fig 1 —Diagrammatic representation of the various congenital abnormalities of the heart and great vessels *I. 1*, pulmonic stenosis; *2*, pulmonary hypertension; *3*, coarctation of aorta, *4*, aortic stenosis *II: 1*, ventricular septal defect, *2*, atrial septal defect; *3*, aberrant pulmonary vein, *4*, patent ductus arteriosus, *5*, mitral regurgitation, *6*, aortic regurgitation; *7*, tricuspid regurgitation *III* physiologic single ventricle (large ventricular septal defect, transpositions, truncus arteriosus)

The third category (Figs 1 and 2,*III*) in-

Congenital Malformations of the Heart with Correlation of the Clinical and Physiologic Features

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Introduction

In the past 15 years major and fundamental accumulations of knowledge concerning circulatory disorders produced by congenital lesions have been acquired primarily because of technical advancements available to the clinical investigator Important among these have been technics for the measurement of hemodynamic abnormalities afforded by cardiac catheterization, the application of dilution technics to the study of blood flows and shunts and the possibility of in vivo demonstration of anatomic defects of the circulation afforded by angiocardiography As part of the development of the field of thoracic surgery, technics have been devised and applied for the correction of many of the congenital defects of the circulation. This concomitant surgical interest has made necessary not only descriptive physiologic studies but diligent inquiry into the natural physiologic history of these abnormalities

The translation of these physiologic data into clinical terms has made possible considerable rationality and precision in the diagnosis and management of patients with congenital cardiovascular disorders This has been because of the appreciation of the importance of hemodynamic and secondary anatomic factors in the genesis of the history, signs, course and *response* to therapy of these patients The clinical problems presented by a patient with an atrial septal defect, for example, will depend only to a limited *extent* on the anatomy of the interatrial ... to a major extent on the interrelationships of the state of his pulmonary vasculature and right ventricle, the pressure in the pulmonary artery and the resultant direction and quantity of blood flow through the defect. The assessment of a patient with a congenital cardiovascular defect must therefore include a hemodynamic quantitation and not only a simple classification of his cardiac abnormality, since anatomic correction of his circulation may not be salutary and indeed may worsen the state of his cardiovascular function because of the presence of secondary morphologic and hemodynamic changes

What follows is an attempt to present first a basis for understanding the hemodynamic and resultant physical and laboratory abnormalities caused by congenital lesions of the heart and circulation, and second to present a convenient approach to the assessment of patients with these disorders based on the physiologic abnormalities present

It is not our purpose to present a systematic description of each type of congenital heart disease since this approach is most adequately covered elsewhere; the studies of Taussig,[9] Kjellberg,[7] and others[1, 3, 4] should be consulted. The special technics for the study of the circulation are discussed elsewhere in this volume We have included several specific applications of these technics in an appendix to this chapter

Circulatory Abnormalities

Although the physiologic abnormalities responsible for the clinical syndromes accompany-

ing a congenital cardiovascular disorder are usually quite clear when each is studied systematically, the unraveling and understanding of problems presented by a particular patient may be quite complex, indeed, the natural history of the disease is most important. The complexity arises in considerable part because of the frequent coexistence of different kinds and combinations of abnormal circulatory loads, in contrast to the situation usually encountered in a patient with acquired heart disease where one abnormality or load is responsible for the clinical syndrome. In a study of a patient with congenital heart disease one may be confronted, for example, with the task of assessing the combined effects of the pressure work load of pulmonic stenosis and the volume work load of an intracardiac shunt on the ventricles together with the physiologic aberrations produced by chronic arterial hypoxemia. In the present section, we shall attempt to describe first what each of the various congenital abnormalities represents in terms of an abnormal load on the circulation and, second, to discuss the clinical evidences of these physiologic loads We should like to emphasize that in this section we are concerned with the specific anatomy of congenital abnormalities only in so far as it affects the hemodynamic consequences of a lesion, e g , whether or not the aorta is dextropositioned in a patient with a high ventricular septal defect is not at present pertinent

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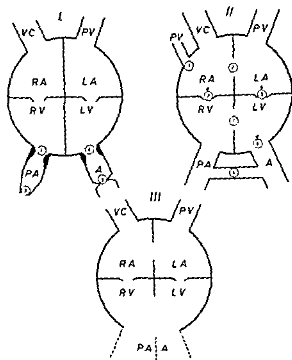


FIG. 1.—Diagrammatic representation of the various congenital abnormalities of the heart and great vessels *I. 1*, pulmonic stenosis, *2*, pulmonary hypertension, *3*, coarctation of aorta, *4*, *aortic stenosis* *II. 1*, ventricular septal defect, *2*, atrial septal defect; *3*, aberrant pulmonary vein, *4*, patent ductus arteriosus, *5*, mitral regurgitation, *6* aortic regurgitation, *7*, tricuspid regurgitation *III* physiologic single ventricle (large ventricular septal defect, transpositions, truncus arteriosus)

also into the right ventricle The right ventricle ejects not only the blood which has flowed into it during diastole from the right atrium but also the increased amount of blood which enters it from the left ventricle during systole In the presence of an atrial septal defect (*II-2*) or aberrant pulmonary veins (*II-3*), the right ventricle ejects an increased amount of blood which has flowed into it during diastole In patent ductus arteriosus (*II-4*), the left ventricle ejects the increased amount of blood which bypasses the systemic circulation through the ductus to the pulmonary artery and thence back to the left atrium. In mitral (*II-5*) and tricuspid (*II-7*) *regurgitation the* downstream ventricle ejects blood not only into its arterial outflow but also back through its regurgitant atrioventricular valve Aortic regurgitation (*II-6*) presents a similar load.

The third category (FIGS. 1 AND 2,*III*) in-

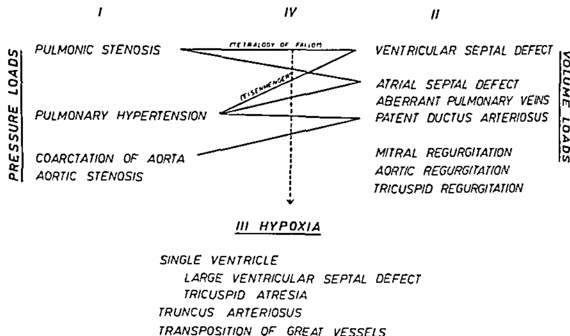


FIG 2 —Hemodynamic abnormalities imposed by the various congenital lesions (see text)

cludes those lesions in which the fundamental abnormality is arterial hypoxia resulting from *systemic venous blood entering the systemic* arterial circulation without having passed through the pulmonary capillaries These lesions include truncus arteriosus, tricuspid atresia, transpositions of the great vessels and single ventricle. Physiologically, each is a variant of a single ventricle in that the two ventricles are in free communication The free communication between the pulmonary and systemic circulations ordinarily results in a considerably lower than normal partial pressure of oxygen in the systemic arterial blood Furthermore, since the right ventricular pressure must be similar to that in the left ventricle, the right ventricle is subjected to a pressure load

The fourth (FIG 2,*IV*) and most difficult category consists of combinations of these pressure and volume work loads. Familiar examples are the combinations of various degrees of pulmonic stenosis with ventricular septal defects of various size (tetralogy of Fallot), the presence of an atrial septal defect in a patient with valvular pulmonic stenosis and the combination of pulmonary hypertension with ventricular septal defect (Eisenmenger's syndrome) The majority of these combinations result in arterial hypoxemia.

The severity of these congenital lesions in a physiologic sense has several determinants In *each of the disorders imposing* an increased pressure work load (FIG. 1,*I*), the severity of the lesion is determined anatomically by the cross sectional area and to a lesser extent the length of the constriction which together offer resistance to the flow of blood With a given anatomic defect, physiologic severity, i e , the pressure abnormality, is determined by the volume of flow through the constriction This relationship is diagrammed in FIGURE 3 where

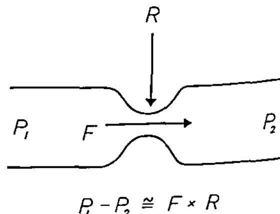


FIG 3 —The relationship between the pressure gradient *across a resistance (R) in the* circulation to the rate of blood flow (*F*) through the obstruction where P_1 = pressure upstream from the resistance and P_2 = pressure downstream from the resistance

P_1 is the pressure upstream from the obstruction, P_2 is the pressure downstream, F is the flow through the obstruction and R is the resistance offered by the obstruction It is evident that, in general terms, the more rapid the blood flow through the resistance the higher will be the pressure proximal to the lesion and hence the pressure work load on the upstream ventricle

The magnitude of the stroke volume work load in lesions causing volume loads (Fig. 1,*II*) is determined by the volume of flow through the defect; this volume is in turn related to the size of the defect and the relationship of the resistances to the outflow of blood from the abnormally connected chambers In the presence of an atrial septal defect, blood commonly flows from left atrium to right atrium during ventricular diastole, since the resistance to outflow of blood into the right ventricle from the right atrium is less than the resistance of outflow of blood from the left atrium to the left ventricle because of the greater distensibility of the right ventricle As a consequence of this, an abnormal volume work load is placed on the right ventricle, and pulmonary flow is abnormally greater than systemic blood flow. With abnormal pulmonary venous insertion into the vena cavae or right atrium, the volume of right ventricular output and increased pulmonary flow will be determined by the number of pulmonary veins inserting aberrantly. The size of a ventricular septal defect is of great importance in determining the volume of the shunt which occurs across it, since normally the pressure in the right ventricle is about one-sixth of that in the left ventricle The fact that both ventricles are subject to a volume load in this disorder has been mentioned. Similarly, in a patent ductus arteriosus, the diameter and the length of the abnormal communication (the resistance offered by it to blood flow) is of paramount importance in determining the magnitude of the left-to-right shunt since the pressure in the aorta is greater than that in the pulmonary artery throughout the cardiac cycle. The left ventricle bears the excess volume load imposed by a patent ductus arteriosus.

The physiologic load imposed by these volume load lesions may be considerably altered by the coexistence of a lesion causing a pressure load (Fig. 2,*IV*). It has been noted that the resistance to the outflow of blood from abnormally connected chambers plays an important role in the magnitude of flow through the abnormal communication. If pulmonic stenosis and an atrial septal defect coexist, for example, the resulting right ventricular hypertension and consequent right ventricular hypertrophy will elevate the resistance to outflow of blood from the right atrium to the right ventricle and tend to decrease the left-to-right shunt; indeed, a right-to-left shunt of blood may develop under these circumstances with the development of a volume load on the left instead of the right ventricle. It must also be recognized that the greater the stroke volume the right ventricle must eject when these two lesions coexist, the higher will be the right ventricular systolic pressure (Fig. 3).

One of the most important factors in determining outflow resistance of blood from the right chambers of the heart is the pulmonary vascular resistance. Ordinarily, the resistance offered by the pulmonary vasculature is approximately one-sixth that of the systemic arterioles; with equal blood flows, normally the pressure in the pulmonary artery is approximately one-sixth that in the systemic circulation If the pulmonary vascular resistance is abnormally increased, the consequent right ventricular hypertrophy in response to the pressure load results in an increased outflow resistance and hence in a decreased left-to-right shunt with an atrial or ventricular septal defect In the presence of patency of the ductus arteriosus, the consequent elevation of pulmonary arterial pressure will result in a decrease in left to-right shunt. The flow and pressure abnormalities existing in any patient at any point in the natural history of his disease and hence the clinical syndrome presented may largely be determined by the state of the pulmonary vasculature. Since the pulmonary vascular resistance is of such major importance in the presence of an abnormal intravascular communication, the characteristics of this pressure load and its changes must be clear.

In patients with lesions in category III (Figs.

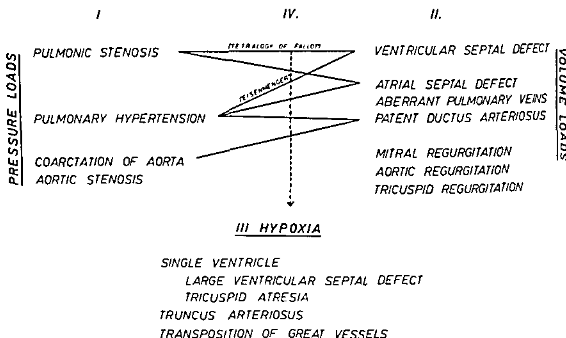


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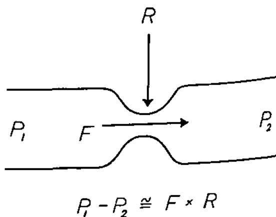


FIG 3—The relationship between the pressure gradient across a resistance (R) in the circulation to the rate of blood flow (F) through the obstruction where P_1 = pressure upstream from the resistance and P_2 = pressure downstream from the resistance

Fig 4 —Right ventricular hypertrophy in a pressure loaded right ventricle, (*left*) P A view, (*right*) left lateral view



Fig 5 —Left ventricular hypertrophy in a pressure loaded left ventricle, (*left*) P A view, (*right*) left anterior oblique view

1 AND 2) where a physiologic single ventricle exists without pulmonic stenosis, the pulmonary vascular resistance must be approximately equal to the systemic vascular resistance for survival Since in these states the ventricles are essentially in free communication, flow into the pulmonary and systemic circulations will be controlled by the relative resistances offered by these two circuits In the intra-uterine state, the pulmonary resistance is very high and 80 to 90 per cent of the right ventricular output passes from the pulmonary artery to the aorta via the ductus arteriosus. The pulmonary vascular resistance normally drops sharply immediately after birth. If this postnatal decrease in vascular resistance occurs in a patient with a physiologic single ventricle, survival is not possible since the much lower resistance offered by the pulmonary circuit results in much higher pulmonary than systemic flow In a patient with a physiologic single ventricle who survives the neonatal period, the necessary pulmonary hypertension results from a high pulmonary vascular resistance associated with persistence of a fetal type of pulmonary arteriolar endothelium [2, 5] Under these circumstances, systemic and pulmonary vascular resistances, pressures and blood flows are similar

Pulmonary vascular changes resulting in increased resistance may also gradually occur during childhood or adulthood in association with high pulmonary blood flows and result in pulmonary hypertension Once the process begins in the small muscular arterioles of the pulmonary circuit, the vascular resistance may steadily increase In some individuals with physiologic single ventricle in whom the pulmonary vasculature offers less resistance than the systemic vasculature, the acquired type of vascular change may also occur in addition to the persistent fetal type and result in a progressive increase in resistance and pressure Why the progressive arteriolar changes resulting in increased vascular resistance occur is not entirely clear. The fact that they do not develop in some individuals with high pulmonary flows suggests the operation of several factors in their genesis, but most investigators feel that they are in some manner traumatic in origin, since they are considerably more common in older individuals whose pulmonary arterioles have been subjected to high flows over longer periods of time. As has been emphasized, pulmonary arterial pressure at any given vascular resistance is related to the volume of the pulmonary blood flow (FIG 3) Indeed, pulmonary hypertension may exist even in the presence of normal or even decreased pulmonary vascular resistance if pulmonary flow is sufficiently great. Flow hypertension is generally regarded as the major stimulus to the development of the pulmonary vascular changes eventuating in an abnormally increased pulmonary vascular resistance

The consequence of a pressure work load on a ventricle is hypertrophy of myocardial fibers with ordinarily little increase in the size of the heart until some degree of myocardial inadequacy is present On inspection and palpation, bulging of the precordium and a lower parasternal lift are strongly suggestive of right ventricular hypertrophy One must differentiate this from the visible but not usually palpable impulse which may be seen over the pulmonary artery in the second and third left interspaces The detection of right ventricular hypertrophy by percussion is often quite unsatisfactory. In the presence of left ventricular hypertrophy, the maximum impulse is seen and felt at the apex and will be heaving and hyperdynamic in character At times, it may be difficult to differentiate the impulse of the normal left ventricle from that of the hypertrophied ventricle

Since hypertrophy of a ventricle is not necessarily associated with significant enlargement of the cardiac silhouette beyond normal limits, the roentgenographic and fluoroscopic examinations may be only suggestive in cases of hypertrophy without enlargement. In cases of marked right ventricular hypertrophy, the roentgenographic examination will usually disclose an elevation of the apex in the postero-anterior view and narrowing or obliteration of the retromanubrial space in the lateral view (FIG 4) In left ventricular hypertrophy (FIG. 5), the apex may be displaced somewhat downward and laterally and the inflow tract of the ventricle may be visible below the diaphragm. The

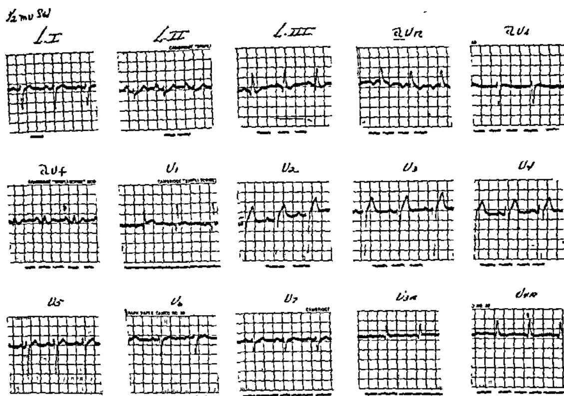


FIG 7 —The electrocardiogram of a patient with a moderately severe pressure load on the right ventricle compatible with right ventricular hypertrophy.

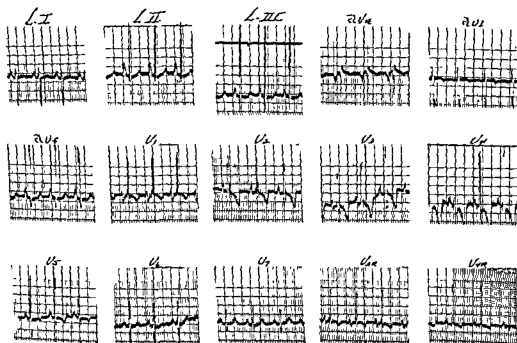


FIG 8 —The electrocardiogram in a patient with a severe pressure load on the right ventricle compatible with marked right ventricular hypertrophy

abnormally acute arc of the left ventricle in the left anterior oblique view is of more importance than overlapping of the spine by the ventricle in this projection

The electrocardiogram is of much greater value in differentiating which ventricle is electrically preponderant since it reflects muscle mass rather than ventricular size In left ventricular hypertrophy caused by a pressure load on the left ventricle, the characteristic electrocardiographic changes associated with this abnormality are regularly seen if the load is of clinically significant severity (FIG 6), the QRS voltage is increased, the QRS forces are usually accentuated at the left ventricle with left axis deviation and a shift of precordial transition to the left and the T waves are inverted in leads aVL, I, V_5 and V_6 In the presence of a right ventricular pressure load, the characteristic changes of right ventricular hypertrophy are usually seen whenever the right ventricular systolic pressure is over half left ventricular systolic pressure. The QRS voltage is increased and rotated more toward the right ventricle with right axis deviation in the limb leads and an increased R/S ratio in precordial leads V_{3R} and V_1. The right precordial pattern tends to show progressively a taller R wave, less S wave and then a qR pattern with increasing pressure (FIG. 7). In more severe hypertension, usually when the right ventricular pressure is greater than the left, the T waves are usually inverted in the right precordial leads and leads aVF and III and a qR pattern is regularly present in V_{3R} and V_1 (FIG 8)

When a ventricle is subjected to a volume load, on the other hand, enlargement and

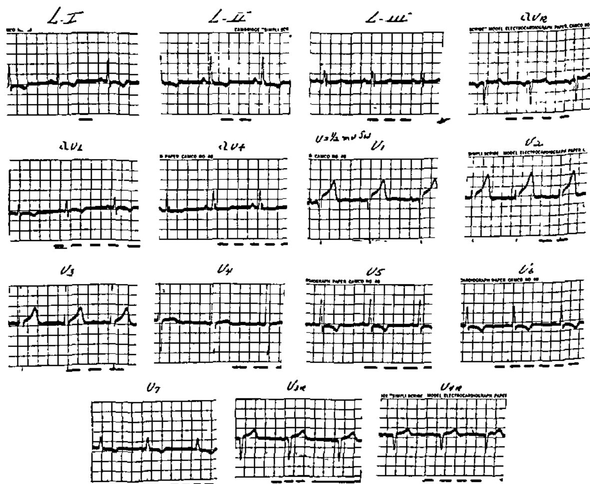


FIG 6.—The electrocardiogram of a patient with a pressure load on the left ventricle com- ... with left ventricular hypertrophy



FIG 10 —Left ventricular enlargement and hypertrophy in a volume loaded left ventricle. (*left*) P A view, (*right*) left anterior oblique view

by most observers when saturation is reduced to 80 to 90 per cent of normal Light exercise in a warm room may make this finding more apparent Below this level cyanosis is commonly more widespread involving the lips, mucous membranes and skin, and the presence of arterial unsaturation will be confirmed by the finding of secondary polycythemia and clubbing of the fingers and toes Several considerations, however, make hazardous the assumptions either of arterial unsaturation as the cause of slight peripheral cyanosis or normal arterial unsaturation in its absence Cyanosis depends on the presence in capillary blood of approximately 5 Gm of unsaturated hemoglobin Therefore, visible cyanosis may occur in the presence of normal arterial saturation if venous unsaturation becomes marked enough to cause capillary unsaturation of this degree Slowing of superficial blood flow due to cold with consequent increase in tissue oxygen extraction with a quite widened arteriovenous oxygen difference (stagnant hypoxia) is an example of this variety of cyanosis and is not uncommonly reported by mothers in their children after swimming A physical examination performed in a cold environment may also rarely result in an erroneous impression of slight arterial unsaturation. Another important cause of stagnant hypoxia with a normal arterial saturation is the slowed peripheral circulation which may accompany heart failure Stagnant hypoxia as a cause of cyanosis should be suspected when the decrease in venous return caused by a tourniquet (including a blood pressure cuff) causes the rapid appearance of cyanosis distal to the point of application. On the other hand, since 5 Gm of unsaturated hemoglobin in the capillaries are necessary for cyanosis to occur, it is obvious that cyanosis cannot occur in severe anemia Finally, it must be remembered that hemoglobin abnormalities (methemoglobinemia, etc.), and other causes of discoloration of the skin (argyria, etc) can superficially stimulate cyanosis Arterial saturation may be quite closely approximated at rest and during

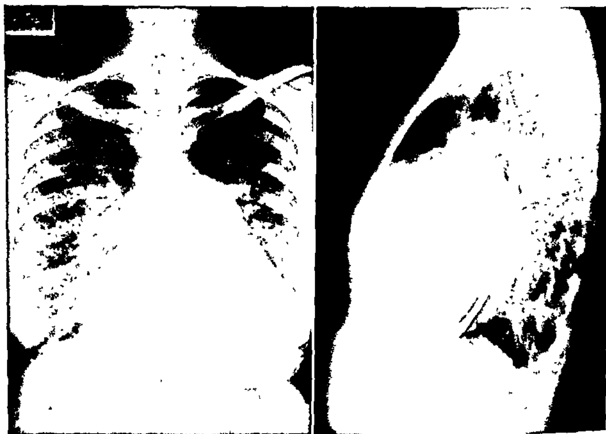


FIG 9 —Right ventricular enlargement in a volume loaded right ventricle, (*left*) P A view, (*right*) left lateral view

hypertrophy tend to occur together In right ventricular volume loads, a precordial bulge is less common than with pressure loads, but a vigorous right ventricular parasternal impulse is usually present In left ventricular enlargement, the apical impulse is usually displaced to the left and downward to the fifth interspace in young children and to the sixth interspace in adults.

Fluoroscopic and roentgenographic examinations are of considerable value under these circumstances, since cardiac enlargement is demonstrable with the characteristic obliteration of the retromanubrial space in right ventricular enlargement (FIG 9) and downward, lateral and posterior extension of the cardiac silhouette in left ventricular enlargement (FIG. 10). The electrocardiogram in the presence of volume-loaded ventricles is variable. In volume loads of the left ventricle, the electrocardiogram may be normal or show nothing more than increased QRS voltage suggestive of left ventricular hypertrophy, often with some slight widening of QRS duration Precordial T waves may be tall and peaked These changes are usually slight, even in the presence of considerable cardiac enlargement If enlargement and hypertrophy of the left ventricle occur together, the electrocardiogram will reflect hypertrophy The electrocardiogram in the volume-loaded right ventricle on the other hand, is reasonably characteristic, with the pattern of "incomplete right bundle-branch block" characterized by slight QRS prolongation, ordinarily not over 0 12 second, and the occurrence of late activation of the right ventricle manifested by S waves in Leads aVL and I and iSR′ in Leads V_{3R}, V_{4R}, V_1 and V_2 (FIG 11). When a volume and a pressure load coexist, the electrocardiogram also has an rSR′ in V_{3R} and V_1 but the secondary R wave is quite tall (FIG. 12)

The clinical consequence of hypoxia is commonly the occurrence of cyanosis A bluish-purple hue to the nail beds is suggestive of arterial unsaturation and usually will be noted

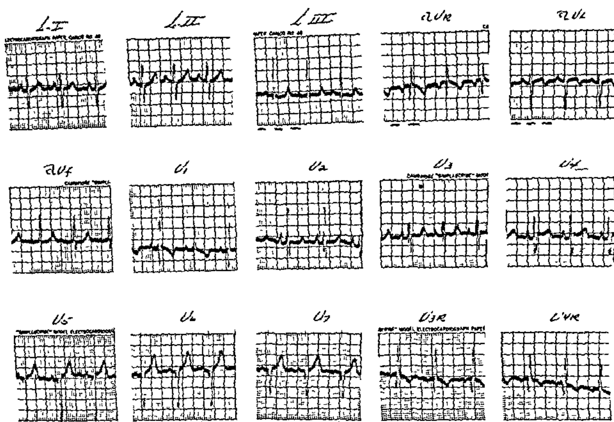


FIG 12.—The electrocardiogram of a patient with a combined pressure and volume loaded right ventricle showing incomplete block and right ventricular hypertrophy

inspired air to hemoglobin When arterial unsaturation is present, the differential diagnosis between veno-arterial shunts and the common causes of abnormalities of oxygen transport (pulmonary insufficiency) can usually be made by the behavior of arterial saturation when the partial pressure of oxygen in the inspired air is increased If arterial saturation is continuously monitored by either an ear or cuvette oximeter while the patient breathes 100 per cent oxygen, a rise in saturation to nearly normal values within 20 seconds suggests pulmonary insufficiency, while a slower and usually negligible increase suggests veno-arterial shunting The hemodynamic changes resulting from oxygen inhalation will be discussed in more detail later

Another consequence of hypoxia is the commonly reduced oxygen consumption (basal metabolic rate) of patients with considerable right to left shunts. In individuals with tetralogy of Fallot, for example, values of −20 to −30 per cent may occur The decreased oxygen supply in the arterial blood is usually compensated for by an increased oxygen extraction in the tissues with resultant marked unsaturation of venous blood rather than by an increase in rate of blood flow. Polycythemia secondary to arterial hypoxia increases the available oxygen per unit of blood and usually occurs when arterial saturation is chronically below about 85 per cent

The frequently key position of the state of the pulmonary circulation in determination of the clinical syndrome presented by patients with congenital heart disease has been stressed. The physical examination and roentgenographic findings are often of considerable help in assessing pulmonary flow and pulmonary vascular pressure. In the presence of increased pulmonary blood flow with normal pulmonary vascular resistance which may occur with left-to-right shunts in the presence of an atrial septal defect or a patent ductus arteriosus, the pulmonary arterial system tends

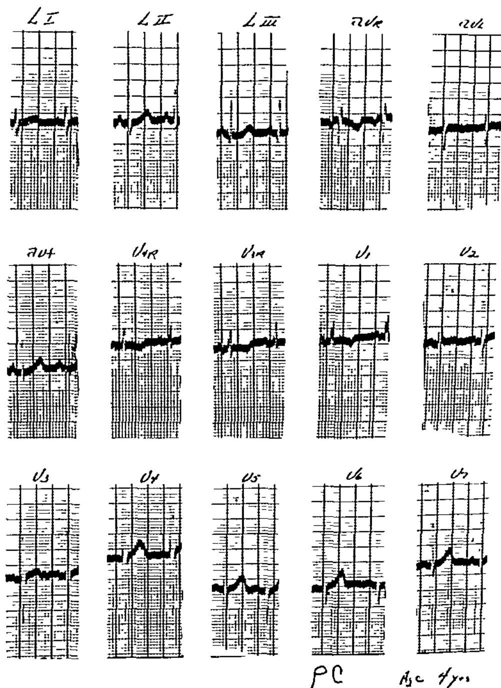


FIG 11 —The electrocardiogram of a patient with a volume loaded right ventricle showing incomplete right bundle-branch block

exercise by the use of an ear oximeter and measured precisely by manometric analysis of an arterial blood sample.

Since in certain congenital abnormalities the portions of the body supplied by the aortic branches either proximal or distal to the left subclavian artery (above or below the pelvic brim) may receive blood of decreased saturation, a careful inspection for differential cyanosis must be made, and often a comparison of the arterial saturation in the right brachial artery (or ear) and a femoral artery (or scrotum using the ear oximeter) will be necessary

The presence of normal arterial saturation at rest and during exercise and the absence of a history of cyanosis exclude the presence of veno-arterial shunts in the heart or lungs and abnormalities of the transport of oxygen from

auscultation will reveal a loud and often single, pure second sound at the pulmonic area. On roentgenographic examination, the central pulmonary arteries in pulmonary hypertension commonly appear enlarged, not unlike those seen with increased pulmonary flow without pulmonary hypertension. The characteristic difference between pulmonary hypertension and increased pulmonary blood flow is to be found in the more peripheral portions of the lung fields which in pulmonary hypertension tend to be of normal to decreased vascularity. Careful inspection will commonly disclose a sharp decrease in caliber of the pulmonary arteries as they pass through the central portions of the lung fields On fluoroscopic examination, pulsation of the pulmonary arteries, especially the tertiary branches, is commonly less in pulmonary hypertension The pulmonary arterial flow and the pulmonary arterial pressure must be measured by cardiac catheterization and pulmonary resistance calculated Quantitation of pulmonary flow, pressure and resistance in this manner is essential for evaluation of patients suspected of having deviations in pulmonary circulation from normal

Evaluation of the systemic circulation is ordinarily considerably simpler The presence of a markedly narrowed pulse pressure in the brachial artery suggests either an obstructive aortic valvular lesion or the presence of the increased total systemic resistance and decreased stroke volume which may accompany myocardial inadequacy. The presence of hypertension in the upper extremities and normal to decreased pressure in the lower extremities is pathognomonic of the presence of a postductal coarctation of the aorta. An abnormally widened pulse pressure is seen in any lesion in which the outflow from the systemic arterial system is abnormally rapid, such as patent ductus arteriosus, aortic regurgitation, aortic window or communication of a sinus of Valsalva with the right side of the heart The absence of these abnormalities, even on direct measurement of arterial pressure, does not, however, exclude the presence of these various lesions. Systemic blood flow and resistance calculations obtained by cardiac catheterization for comparison with pulmonary blood flow and resistance calculations are crucial for evaluation of patients with congenital heart disease

Evaluation of a Patient

The diagnostic approach to a patient with a congenital cardiovascular disorder should eventuate in a diagnosis which includes not only the probable anatomic abnormality but also, of equal importance, the nature and extent of the hemodynamic abnormalities The consequences of these abnormalities, as has been emphasized, are to be found in data from the history, the physical examination, the roentgenographic and fluoroscopic examinations, and the electrocardiograms of a patient. Certain of the data obtained from these examinations may, however, be of little value in arriving at a satisfactory anatomic-hemodynamic diagnosis A heart murmur, for example, may suggest the presence of a particular lesion but usually is not of value in assessing the hemodynamic disturbances of the circulation. We have, therefore, found it useful to use first those data which reflect the circulatory abnormalities accompanying the various lesions in the evaluation of an individual patient Arterial oxygen saturation, ventricular size and preponderance, pulmonary and systemic blood flows and pressures as estimated from the various examinations, when used in a deductive sequence, will permit a reasonably complete anatomic and physiologic assessment An evaluation flow sheet is presented in Table 1 in which these commonly available data are used as separators.

The first major subdivision is based on the presence or absence of arterial unsaturation Patients who are acyanotic (*Groups 1-7*) are then subdivided into 4 categories based on the electrocardiographic estimate of ventricular size and preponderance, namely, left ventricular hypertrophy (*1 and 2*) normal (*3*), incomplete right bundle-branch block (*4*) or right ventricular hypertrophy (*5-7*) These are then subdivided into groups by the roentgenologic findings.

Group 1

In acyanotic patients with evidence of a pressure load on the left ventricle manifested by

to be diffusely enlarged. On physical examination, a prominent early systolic click can often be heard over an enlarged pulmonary artery. The enlargement of the main pulmonary artery and all of its branches in roentgenographic films extends diffusely throughout the lung fields (FIGS. 9 AND 10). When prominent vascular markings are noted in the costophrenic angles on oblique views of the chest, it may be assumed that the pulmonary blood flow is increased. Fluoroscopy is of greater value, since the degree of systolic expansion of the vessels can be evaluated. Definitely increased pulsation of the vessels in the midthird of the right lung field is pathonomonic of increased pulmonary blood flow.

A decrease in pulmonary blood flow is characterized by unusually radiolucent lung fields and vascular markings which are less prominent than normal (FIGS. 4 AND 13). The main pulmonary artery may, however, be enlarged due to poststenotic dilatation beyond a narrowed pulmonic valve (FIG. 4). A decreased pulmonary blood flow is uncommonly seen unless pulmonary blood flow is less than systemic flow, i.e., unless a right-to-left shunt is present. Decreased pulmonary flow thus characterizes any condition in which there is obstruction to inflow of blood into the pulmonary artery and a communication between the venous and arterial circulation with right-to-left shunt. Examples include pulmonic stenosis with a ventricular septal defect or atrial septal defect and truncus arteriosus with small pulmonary arteries arising from the common trunk (FIG. 13).

The pressure in the pulmonary artery is somewhat more difficult to assess. This is especially true when minor to moderate degrees of increased pulmonary vascular resistance and increased blood flow (left-to-right shunt) are both factors in pulmonary hypertension. In pulmonary hypertension with approximately equal pulmonary and systemic blood flows, the physical examination usually discloses a palpable shock over the second left interspace coincident with the second heart sound, and



FIG. 13.—The roentgenogram from a patient with a truncus arteriosus, (*left*) P.A. view, (*right*) left lateral view.

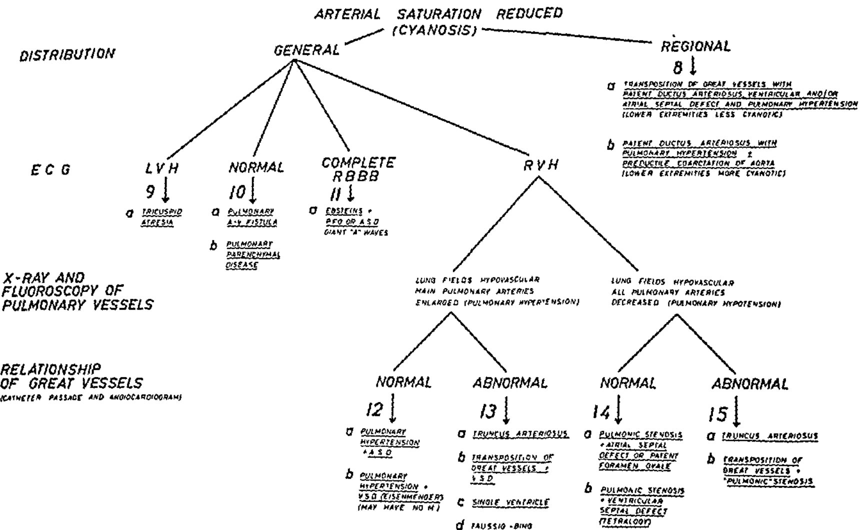
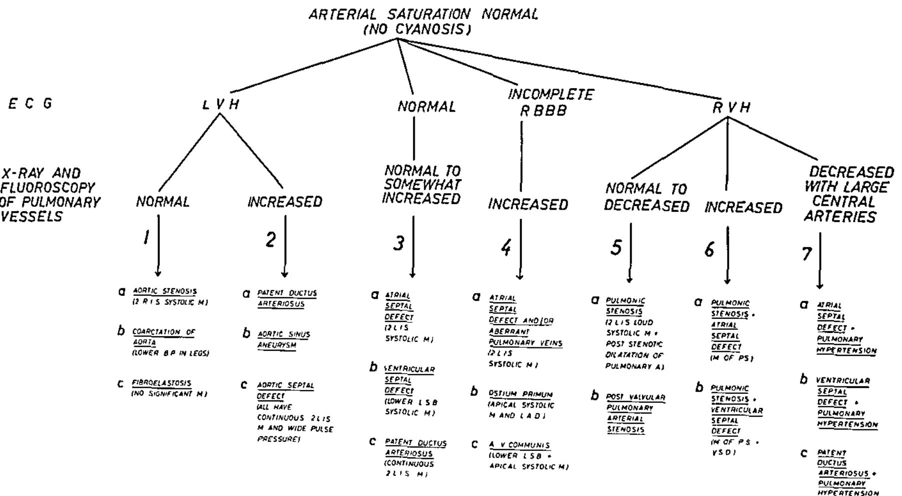
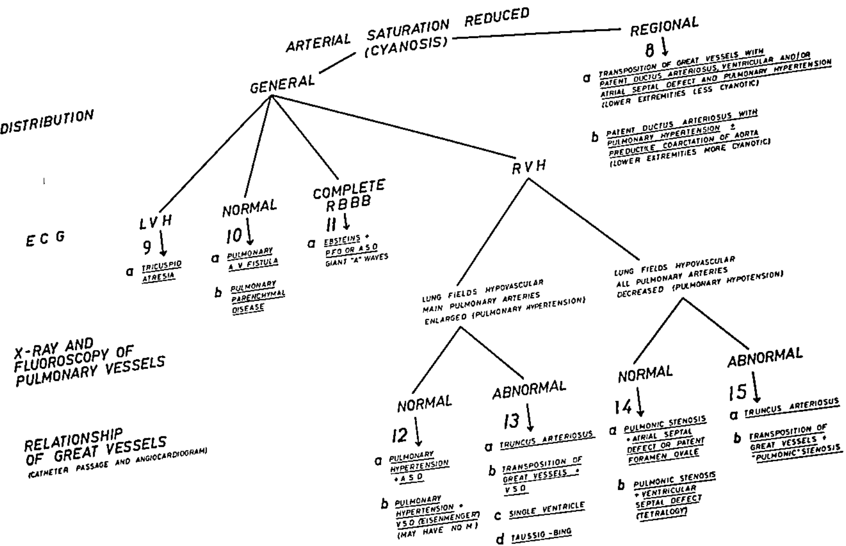

ARTERIAL SATURATION REDUCED (CYANOSIS)
DISTRIBUTION
GENERAL
REGIONAL
8
a TRANSPOSITION OF GREAT VESSELS WITH PATENT DUCTUS ARTERIOSUS, VENTRICULAR AND/OR ATRIAL SEPTAL DEFECT AND PULMONARY HYPERTENSION (LOWER EXTREMITIES LESS CYANOTIC)
b PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION ± PREDUCTILE COARCTATION OF AORTA (LOWER EXTREMITIES MORE CYANOTIC)
E C G
L V H
9
a TRICUSPID ATRESIA
NORMAL
10
a PULMONARY A-V FISTULA
b PULMONARY PARENCHYMAL DISEASE
COMPLETE RBBB
11
a EBSTEINS + PFO OR A S D GIANT "A" WAVES
R V H
X-RAY AND FLUOROSCOPY OF PULMONARY VESSELS
LUNG FIELDS HYPOVASCULAR MAIN PULMONARY ARTERIES ENLARGED (PULMONARY HYPERTENSION)
LUNG FIELDS HYPOVASCULAR ALL PULMONARY ARTERIES DECREASED (PULMONARY HYPOTENSION)
RELATIONSHIP OF GREAT VESSELS
(CATHETER PASSAGE AND ANGIOCARDIOGRAM)
NORMAL
12
a PULMONARY HYPERTENSION + A S D
b PULMONARY HYPERTENSION + V S D (EISENMENGER) (MAY HAVE NO M)
ABNORMAL
13
a TRUNCUS ARTERIOSUS
b TRANSPOSITION OF GREAT VESSELS + V S D
c SINGLE VENTRICLE
d TAUSSIG - BING
NORMAL
14
a PULMONIC STENOSIS + ATRIAL SEPTAL DEFECT OR PATENT FORAMEN OVALE
b PULMONIC STENOSIS + VENTRICULAR SEPTAL DEFECT (TETRALOGY)
ABNORMAL
15
a TRUNCUS ARTERIOSUS
b TRANSPOSITION OF GREAT VESSELS + "PULMONIC" STENOSIS

TABLE 1.—*Flow Sheet for the Evaluation of a Patient with Congenital Heart Disease*




ARTERIAL SATURATION REDUCED (CYANOSIS)
DISTRIBUTION
GENERAL
REGIONAL
8
a TRANSPOSITION OF GREAT VESSELS WITH PATENT DUCTUS ARTERIOSUS, VENTRICULAR AND/OR ATRIAL SEPTAL DEFECT AND PULMONARY HYPERTENSION (LOWER EXTREMITIES LESS CYANOTIC)
b PATENT DUCTUS ARTERIOSUS WITH PULMONARY HYPERTENSION ± PREDUCTILE COARCTATION OF AORTA (LOWER EXTREMITIES MORE CYANOTIC)
E C G
L V H
9
a TRICUSPID ATRESIA
NORMAL
10
a PULMONARY A V FISTULA
b PULMONARY PARENCHYMAL DISEASE
COMPLETE R B B B
11
a EBSTEINS + P.F.O OR A S D GIANT "A" WAVES
R V H
X-RAY AND FLUOROSCOPY OF PULMONARY VESSELS
LUNG FIELDS HYPOVASCULAR MAIN PULMONARY ARTERIES ENLARGED (PULMONARY HYPERTENSION)
LUNG FIELDS HYPOVASCULAR ALL PULMONARY ARTERIES DECREASED (PULMONARY HYPOTENSION)
RELATIONSHIP OF GREAT VESSELS (CATHETER PASSAGE AND ANGIOCARDIOGRAM)
NORMAL
12
a PULMONARY HYPERTENSION + A S D
b PULMONARY HYPERTENSION + V S D (EISENMENGER) (MAY HAVE NO M)
ABNORMAL
13
a TRUNCUS ARTERIOSUS
b TRANSPOSITION OF GREAT VESSELS + V S D
c SINGLE VENTRICLE
d TAUSSIG - BING
NORMAL
14
a PULMONIC STENOSIS + ATRIAL SEPTAL DEFECT OR PATENT FORAMEN OVALE
b PULMONIC STENOSIS + VENTRICULAR SEPTAL DEFECT (TETRALOGY)
ABNORMAL
15
a TRUNCUS ARTERIOSUS
b TRANSPOSITION OF GREAT VESSELS + "PULMONIC" STENOSIS

left ventricular hypertrophy and normal pulmonary vessels, one of several conditions may be responsible. The diagnosis of aortic stenosis (*a*) is made by the characteristic loud, harsh, systolic ejection murmur and thrill maximally heard *in the second right interspace, ordinarily* transmitted well to the vessels of the neck An early systolic click is almost always present at the apex, at the third and fourth left interspaces parasternally and at the base in mild and moderately severe cases The second sound in the aortic area is usually normal, or may even be accentuated in mild or moderate cases, but, with more severe pressure gradients across the aortic valve, may be markedly reduced. Phonocardiography usually reveals the characteristic diamond-shaped systolic ejection murmur with maximum intensity in midsystole The stenosis may be either valvular or subvalvular The differential diagnosis is very difficult to make even with all available diagnostic technics. It should be emphasized that even in the presence of a characteristic murmur of considerable intensity (if the patient does not fall into the first category of this grouping, when evidence of a pressure load on the left ventricle is not present), physiologically significant aortic stenosis is quite unlikely. In a patient in *Group 1*, the pressure gradient and flow across the aortic valve must be determined at left heart catheterization

Simple postductal ("adult") coarctation of the aorta (*b*) is readily diagnosed by the existence of a pressure gradient across the coarctation as measured by a difference in the blood pressure recorded in the arms and legs. Uncommonly, the hypertension may exist only in the right arm if the left subclavian artery is involved in the coarctation The femoral, popliteal, posterior tibial, and dorsalis pedis pulses may be considerably reduced to absent. The mean arterial blood pressure below the coarctation may be normal and is commonly only slightly reduced as measured directly in the femoral artery; the absence of an indirect blood pressure is due to the markedly decreased pulse pressure. Blood flow in the legs is maintained by liberal collateral circulation via the internal mammary vessels, the subscapular arteries and other branches of the subclavian arteries. These enlarged collateral vessels may produce bilateral notching in the third to eighth ribs, usually only after the age of 5 to 7 in children, and in adults. Bruits may be audible over these vessels. A nonspecific systolic murmur is commonly heard over the anterior and more often the posterior thorax between the scalpulae. A continuation of this murmur may be heard occasionally into diastole, but in our experience this has always occurred when there was a considerable difference between the mean pressure in the lower and upper extremities.

Finally, an occasional patient in this group will have no abnormalities of blood pressure and no significant murmur The diagnosis of fibroelastosis (*c*) should be suspected.

Group 2

In the presence of left ventricular hypertrophy with roentgenographic evidence of increased pulmonary flow, a volume load on the left ventricle is probable This may be caused by an abnormal shunt between the aorta and the pulmonary artery via a patent ductus arteriosus (*a*) or an aortic septal defect (*c*) or the aorta and the right atrium or ventricle through an aortic sinus aneurysm or a coronary arteriovenous fistula (*b*) The clinical findings are similar in that a characteristic crescendo-decrescendo continuous murmur across the second heart sound (best heard in the second left interspace parasternally) is present, this murmur often may be heard well out to the midclavicular line and down the left sternal border A widened systemic arterial pulse pressure, especially during exercise, is also commonly found with each of these lesions. A faint apical and lower precordial mid-diastolic rumbling murmur caused by increased mitral valve flow is common in patent ductus arteriosus. The differential diagnosis among these lesions may be made presumptively at cardiac catheterization. Arterialization of pulmonary arterial blood compared with right ventricular blood is found with either a patent ductus or an aortic septal defect; the definitive diagnosis may usually be made by retrograde aortography. When an aortic sinus aneurysm communicates with the right ventricle, arterialization of this chamber compared with the right

atrium will be found, and in the rare instance of communication with the right atrium, arterialization of this chamber compared with the vena cavae is diagnostic.

Group 3

A large group of patients suspected of having congenital heart disease sometimes present a normal arterial oxygen saturation, no evident ventricular hypertrophy or enlargement and approximately normal (questionably increased) pulmonary flow on clinical examination In this group are patients with a physiologically small atrial septal defect (*a*) or a small ventricular septal defect (*b*) or a patent ductus arteriosus (*c*).

The suspicion of atrial septal defect in this category of patients is usually raised by the finding of a slight or moderate murmur of innocent characteristics heard at the second and third left interspaces parasternally with constant splitting of the second sound in that area. At cardiac catheterization, significant arterialization of blood in the right atrium over that found in a vena cava will usually be noted, but occasionally the left-to-right shunt may be so small that the nitrous oxide test must be used (see Appendix).

A ventricular septal defect of small size is characterized by a quite loud and long systolic murmur best heard in the third and fourth interspaces parasternally on the left, characteristically the murmur is heard best in the fourth and fifth spaces when the patient stands. *It is quite* common in this group of patients with ventricular septal defect to find no or only equivocal changes in arterialization of right ventricular blood, and determination of the time concentration of nitrous oxide in the right ventricle and pulmonary artery may be necessary. The diagnosis of patent ductus is made by the characteristic murmur and arterialization of pulmonary arterial blood.

It should be emphasized that in these patients with normal arterial saturation and no ventricular hypertrophy or enlargement and with normal to slightly increased pulmonary flows the lesion is hemodynamically of little significance.

Group 4

Another large group of patients have evidence of a volume load on the right ventricle suggested by the finding of incomplete right bundle branch block in the electrocardiogram and roentgenographic and fluoroscopic evidence of increased pulmonary blood flow. The anatomic abnormality in this group is a left to right shunt via an atrial septal defect and/or aberrant pulmonary veins (*a*), an atrial septal defect of the *ostium primum* variety (*b*) or a variant of the arteriovenous communis defect (*c*).

In a patient in this group with an atrial septal defect with or without aberrant insertion of pulmonary veins to the right atrium, the left to right shunt may be marked with pulmonary flow as much as three to four times systemic flow. The diagnosis is readily made by cardiac catheterization. Although aberrant insertion of pulmonary veins into the right atrium is almost always accompanied by an atrial septal defect, rarely the atrial septal defect may be absent. Since the abnormality of oxygen content of the chambers of the right side of the heart is the same whether or not the atrial septal defect accompanies the aberrant pulmonary veins, catheter passage into the left atrium must always be attempted to prove the existence of the defect in the atrial septum. If the catheter cannot be passed into the left atrium, the vigorous insertion of indocyanine dye into the right atrium with the catheter directed toward the atrial septum will usually result in an early circulation peak.

Other patients in this category may have a more extensive abnormality of the cardiac septum, an ostium primum defect, or in addition, an arteriovenous communis defect with an ostium primum defect of the lower portion of the atrial septum and a defect in the upper portion of the ventricular septum, often associated with an abnormality of the mitral valve with consequent mitral regurgitation or even a common atrioventricular valve. An ostium primum defect without involvement of the mitral valve cannot be differentiated from the more common ostium secundum variety of atrial septal defect If the mitral valve is in-

left ventricular hypertrophy and normal pulmonary vessels, one of several conditions may be responsible The diagnosis of *aortic stenosis* (*a*) is made by the characteristic loud, harsh, systolic ejection murmur and thrill maximally heard in the second right interspace, ordinarily transmitted well to the vessels of the neck. An early systolic click is almost always present at the apex, at the third and fourth left interspaces parasternally and at the base in mild and moderately severe cases The second sound in the aortic area is usually normal, or may even be accentuated in mild or moderate cases, but, with more severe pressure gradients across the aortic valve, may be markedly reduced. Phonocardiography usually reveals the characteristic diamond-shaped systolic ejection murmur with maximum intensity in midsystole The stenosis may be either valvular or subvalvular The differential diagnosis is very difficult to make even with all available diagnostic technics It should be emphasized that even in the presence of a characteristic murmur of considerable intensity (if the patient does not fall into the first category of this grouping, when evidence of a pressure load on the left ventricle is not present), physiologically significant aortic stenosis is quite unlikely. In a patient in *Group 1*, the pressure gradient and flow across the aortic valve must be determined at left heart catheterization.

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a patient is not different from that of a patient with pulmonic stenosis and an intact atrial septum (*Group 5a*); the diagnosis must be established by catheterization

In the unusual patient with pulmonic stenosis and a ventricular septal defect who has only a left-to-right shunt the physical examination will suggest the diagnosis because of the presence of the murmur of ventricular septal defect A patient in this group usually has an infundibular rather than a valvular pulmonic stenosis ("acyanotic tetralogy of Fallot") The diagnosis is readily made at cardiac catheterization

Group 7

The last category of acyanotic patients includes those who have evidence of a pressure load on the right ventricle associated with evidence of both pulmonary hypertension and increased pulmonary flow on roentgenographic and fluoroscopic examinations, the central pulmonary arteries are quite enlarged and a rather sharp reduction in caliber to vessels which are normal to a decrease in size, usually occurs in the middle of the lung fields, the pulsations of all of the vessels tend to be increased, however, when both flow and pressure are high An atrial (*a*) or ventricular (*b*) septal defect or a patent ductus arteriosus with a left-to-right shunt plus pulmonary arteriolar disease with increased resistance to pulmonary blood flow will usually be found The pulmonary hypertension in this group is thus the consequence of an increase in both pulmonary flow and resistance (Fig 3) The differential diagnosis is sometimes quite difficult to make on clinical examination because of changes in the characteristic auscultatory findings caused by the coexistent pulmonary hypertension The second sound at the pulmonic area is increased and usually narrowly split

In a patient with atrial septal defect, the electrocardiogram may reflect both the pressure and volume load with a rSR′ pattern in V_{3R} and V_1, the initial r wave is quite small and the R′ deflection is tall (Fig 12) The ventricular septal defects which appear in this category are usually moderately large and involve both the muscular and membranous portions of the ventricular septum The murmur is commonly not as loud as that heard in group 3 patients. The patients with a patent ductus arteriosus may have a considerably shorter murmur with only a faint, early diastolic component; the electrocardiogram may be compatible with some degree of left as well as right ventricular hypertrophy characterized by an R/S or R/s deflection in leads V_{3R} and V_1 instead of a qR pattern and less right axis deviation in the limb leads

The other major subdivision of patients with congenital heart disease includes all of those patients who have systemic arterial unsaturation (*Groups 8-16*) The differential diagnosis of the anatomic and hemodynamic abnormalities in cyanotic patients is often more difficult and usually depends to a major extent on elaborate diagnostic methods.

Group 8

The first step in diagnosis of a cyanotic patient is careful inspection to determine whether or not the cyanosis is generalized In certain individuals, the lower extremities are less cyanotic than the upper extremities These patients (*a*) all have transposition of the great vessels, a large ventricular septal defect, a patent ductus arteriosus and pulmonary hypertension with the fetal type of pulmonary arteriole, usually a preductile coarctation is present. The pulmonary artery arises from the left ventricle and hence is carrying arterialized blood which passes through the ductus arteriosus to the distal aorta to the lower portion of the body The circulation to the upper portion of the body, on the other hand, arises from the aorta which in turn arises from the right ventricle and hence receives venous blood The change in the degree of cyanosis is usually noted at the level of the pelvis since the mammary arteries supplying the trunk arise from the subclavian arteries which receive blood from the aorta proximal to the entrance of the ductus arteriosus

In certain other individuals, it will be noted that the right arm and head or, indeed, the entire trunk may be less cyanotic than the legs, and the fingers of the right hand or both hands may be less clubbed than the toes If arterial

volved, the murmur of mitral regurgitation will often be heard and left axis deviation will be present in the limb leads of the electrocardiogram in addition to the incomplete right bundle-branch block In a more extensive arteriovenous communis defect a ventricular septal defect may be suspected when a characteristic murmur is heard and demonstrated either by further arterialization of the blood in the right ventricle over that in the right atrium or by catheter passage through the defect

In these patients some degree of pulmonary hypertension may be found but it is usually due primarily to the great volume of pulmonary blood flow associated with the left-to-right shunt; the pulmonary arteriolar resistance will be found to be essentially normal (see Fig 3)

Group 5

Patients in this category have evidence of a pressure load on the right ventricle in the electrocardiogram with normal to decreased size of the branches of the pulmonary artery caused by an increased resistance to outflow from the right ventricle due to either a valvular or an infundibular pulmonic stenosis In either case, the lesion is characterized by a harsh, short, systolic ejection-type murmur which is usually quite loud and most often associated with a thrill occurring maximally in the second left interspace parasternally The second sound in the pulmonic area is frequently reduced in intensity and may be widely split. When the stenosis is marked, the closing of the pulmonary valves cannot be heard at all, and therefore the second sound in the pulmonic area is unusually pure due to the absence of the usual pulmonic component In cases of moderate to marked valvular pulmonic stenosis, the roentgenogram will reveal, in addition to normal cardiac size and evidence of right ventricular hypertrophy, a poststenotic dilatation of the main pulmonary artery Pulmonary flow is usually normal in these individuals, but since the pressure is often markedly reduced, the lung fields may appear to have a somewhat decreased vascularity. Cardiac catheterization will disclose a pressure gradient across the pulmonic valve in cases of valvular stenosis. In patients with infundibular stenosis, the poststenotic dilatation is commonly absent. Cardiac catheterization will usually disclose two areas of pressure change in infundibular stenosis, one at the pulmonic valve and the other at the entrance to the infundibuular chamber ("third ventricle"). We have seen many patients, however, in whom careful inspection of the pressure tracing reveals no significant change in the systolic or diastolic pressure as the catheter was withdrawn from the pulmonary artery through the infundibular chamber; the only pressure change occurred at the level of the entrance to the infundibular chamber. It is obviously important in the studies to correlate the catheter position with the pressure tracing, or infundibular stenosis will be erroneously called, in these instances, a valvular stenosis. The atrial pressure in severe stenosis often rises markedly during atrial systole due to the increased atrial outflow resistance associated with right ventricular hypertrophy, and a large A wave will be recorded This may be reflected in a large A wave in the jugular venous pulse and also associated with an enlargement of the P wave of the electrocardiogram

In this category also, there will occasionally be found a patient in whom the obstruction to pulmonary flow is located in the pulmonary artery beyond the pulmonic valve (*b*) The diagnosis must be made by cardiac catheterization and confirmed by angiocardiography.

Group 6

Patients in this group have evidence of a pressure load on the right ventricle in the electrocardiogram but have increased size of the pulmonary vessels on roentgenograms and evidence of increased pulmonary flow on fluoroscopic examination Pulmonic stenosis associated with a left-to-right shunt through an atrial septal defect (*a*) or rarely through a ventricular septal defect (*b*) may be present Whenever the right ventricular pressure is below systemic pressure in a patient with pulmonic stenosis and an atrial septal defect, despite the right ventricular hypertrophy consequent to the pressure load, a left-to-right shunt of considerable magnitude may occur through the atrial septal defect The physical examination in such

waves, in the electrocardiogram Generalized moderate cardiac enlargement is characteristically seen in roentgenograms. On auscultation, the heart sounds are often both reduplicated and no distinctive murmur is heard The diagnosis in this group is Ebstein's anomaly of the tricuspid valve in which the valve is incompetent due to malposition of the cusps, resulting in a hemodynamic single right heart chamber (atrium-ventricle) A patent foramen ovale or an atrial septal defect is almost always present and the consequent right to left shunt results in the arterial unsaturation. The abnormal cardiac load is the "tricuspid regurgitation."

In the great majority of patients with congenital heart disease and generalized cyanosis, right ventricular hypertrophy is found in the electrocardiogram (*Groups 12–15*) In all of these patients, right ventricular systolic pressure is equal to or greater than left ventricular systolic pressure because of either severe pulmonary hypertension or an obstruction to outflow from the right ventricle, a major communication exists between the right and left sides of the heart The differential diagnosis among these patients may often be made by dividing them into two categories on the basis of whether or not pulmonary hypertension is present as estimated from the roentgenograms and then subdividing them into groups determined by the relationship of the great vessels. Cardiac catheterization, indicator dilution curves and angiocardiography are usually necessary for the evaluation of these patients

Group 12

In the presence of marked pulmonary hypertension with normal relationship of the great vessels, the arterial unsaturation is the consequence of the intermixing of venous and arterial blood via an atrial septal defect or patent foramen ovale (*a*) or a ventricular septal defect (*b*)

In patients with an interatrial communication in this group there may be no murmur; in those with a ventricular septal defect, a murmur suggesting the lesion may be present, *but* in many is of only slight to moderate intensity and indeed may be absent If there is anatomic dextroposition of the aortic root over the ventricular septum, the defect is classified as the Eisenmenger syndrome. The relationship of the aortic root to the septum cannot be determined clinically, however, and this relationship is of little consequence to the clinician or physiologist

Often little or no left-to-right shunting is found in these patients, and the location of the shunt must be determined by indicator dilution curves.

Group 13

In cyanotic patients with right ventricular hypertrophy and pulmonary hypertension, abnormality of the great vessels may be suspected from the roentgenograms by a concavity of the left upper cardiac border in the region of the pulmonary artery With truncus arteriosus (*a*) the great vessels appear unusually wide in the P A. view (Fig. 13). In patients with truncus arteriosus in this group, i e, with pulmonary hypertension, the pulmonary arteries which originate from the common trunk are quite large. Other patients in this group have complete transposition of the aorta and pulmonary artery with a large ventricular septal defect (*b*) forming functionally a single ventricle (*c*) Others have the Taussig-Bing abnormality (*d*) in which the aorta arises from the right ventricle and the pulmonary artery is only partially transposed, physiologically, a single ventricle exists because of the associated ventricular septal defect

Catheterization of the pulmonary artery in these patients is rarely accomplished, and angiocardiography must be performed to establish the relationship of the vessels.

Group 14

A large group of cyanotic patients with right ventricular hypertrophy will have roentgenographic evidence of pulmonary hypotension and decreased pulmonary flow with apparent normal relationship of the great vessels. Pulmonic stenosis with an interatrial communication (*a*) or a ventricular septal defect (*b*) will be present In the presence of severe pulmonic stenosis, more commonly of the

saturation is greater in the right arm than in the legs, the diagnoses of a preductile coarctation of the aorta and a patent ductus arteriosus may be made. In this condition, the postnatal circulation closely resembles the fetal circulation in that the right ventricle continues to supply blood via the patent ductus arteriosus to the lower half of the body. Ordinarily, the aorta is not completely atretic at the site of coarctation, and some venous blood may reflux from the aorta distal to the coarctation, to the left subclavian, and occasionally even to the left common carotid artery which accounts for the distribution of cyanosis. The pulmonary arterioles in these individuals are characterized by a persistence of the fetal type of endothelium. The pressure in the pulmonary artery, the right ventricle, and the aorta distal to the ductus is the same and ordinarily no lower than in the proximal aorta, collateral vessels do not develop around the coarctation since blood supply to the distal aorta is normal.

In certain patients with patent ductus arteriosus and acquired pulmonary vascular disease (*Group 7c*), the pulmonary disease may become severe enough to result in a reversal of blood flow through the patent ductus because the pulmonary arterial pressure exceeds aortic pressure. The differential diagnosis between this syndrome and the patients in the present group (*8b*) may be quite difficult.

After the diagnosis in patients with regional cyanosis has been suspected, cardiac catheterization, dye dilution curves and angiocardiography will confirm the diagnosis. An angiocardiogram is ordinarily required for the diagnosis of transposition.

Group 9

In cyanotic patients who have electrocardiographic evidence of left ventricular hypertrophy in the limb leads and in the precordial leads, the diagnosis is underdeveloped right ventricle which, in practically all of the cases, is associated with tricuspid atresia. In this abnormality, a large atrial septal defect exists, and blood reaches the pulmonary artery via a ventricular septal defect and/or a patent ductus arteriosus. Left axis deviation may rarely occur in patients with a single ventricle, truncus arteriosus or with the Eisenmenger syndrome, but the precordial leads in these patients regularly show evidence of right ventricular hypertrophy which differentiates them from the syndrome associated with an underdeveloped right ventricle.

Group 10

In certain patients suspected of having congenital heart disease because of generalized cyanosis, no electrocardiographic or clinical evidence of abnormal ventricular size or preponderance will be found. Some of these individuals may have a congenital pulmonary arteriovenous fistula (*a*) in which the arterial unsaturation is due to the communication of small pulmonary arterial branches directly with pulmonary veins. Cyanosis, polycythemia and clubbing are usually marked but disability slight. The usual roentgenogram may show a localized area of increased vascular marking, but an angiogram is necessary to make the diagnosis. Cardiac catheterization is not of positive diagnostic value.

The majority of patients in this category will have pulmonary parenchymal disease (*b*) with an increased alveolar-capillary oxygen gradient. Ordinarily, the presence or absence of parenchymal lung disease of sufficient magnitude to account for an alveolar capillary block syndrome is evident, but in questionable cases the response to the inhalation of 100 per cent oxygen is helpful in differential diagnosis. In the alveolar-capillary block syndrome, if oxygen is administered while the saturation of arterial blood is being monitored by an ear oximeter, a very rapid rise of arterial saturation to normal in less than 20 seconds will ordinarily occur, in the presence of an arteriovenous fistula in the lungs in which unsaturation is due to the communication of the pulmonary artery and vein without exposure of blood to oxygen, the inhalation of oxygen will result in only a slow and slight to moderate rise in arterial saturation.

Group 11

A rare patient with generalized cyanosis will be seen who has complete right bundle-branch block, often accompanied by enlarged "P"

APPENDIX

Special Technics

Catheterization of the right and left sides of the heart, indicator dilution curves and angiocardiography are technics used in the diagnosis and study of heart diseases of many etiologies. A consideration of those details applicable to the study of congenital heart disease will be considered in this section.

Diagnosis of left-to-right shunts. Left-to-right shunts of moderate to major magnitude may be diagnosed by significantly increased oxygen content of blood in the right atrium, right ventricle or pulmonary artery compared with the oxygen content of caval blood. In the unanesthetized child or adult, the oxygen content of inferior vena caval blood is commonly 0.5 to 1.0 volumes per cent higher than that in the superior vena cava. The oxygen content of coronary sinus blood entering the right atrium may be 2 to 3 volumes per cent lower than that of the vena caval blood. In the anesthetized infant or young child, one may uncommonly find a higher oxygen content in superior than in inferior vena caval blood. Because of these variations in oxygen content of blood entering the right atrium and of streaming of blood in this chamber, considerable variation in the oxygen content of samples from different sites may be encountered. A left-to-right shunt may be presumed to be present at atrial level when the oxygen content of this chamber is found to be at least 1.0 volumes per cent greater than the content of both superior and inferior vena caval blood. If only a superior vena caval sample is available, the right atrial content should be over 1.5 volumes per cent greater than superior vena caval blood for diagnosis.

The mixing of venous blood is ordinarily far more nearly complete in the right ventricle. If the oxygen contents of the superior and inferior vena caval and right atrial bloods are less by 1.0 volumes per cent than the blood sampled from the right ventricle, a left-to-right shunt at ventricular level may be presumed to be present. An oxygen content of pulmonary arterial blood greater by 1.0 volumes per cent than that in the right ventricle is presumptive evidence of a left-to-right shunt at pulmonary arterial level.

When contents of the samples obtained at rest are equivocal, samples obtained during exercise or during the inhalation of 100 per cent oxygen, either of which may increase a left-to-right shunt, may help to establish the diagnosis. The use of a well calibrated cuvette oximeter is highly desirable because saturations of multiple samples can be determined and made available during the catheterization, and blood can be reinfused into infants and children. Furthermore, the oxygen saturations so obtained are independent of the amount of dissolved oxygen in the blood which is not the case with manometric analyses. If the diagnosis of a left-to-right shunt remains equivocal on the basis of multiple oxygen saturations, a continuous recording of the saturation of blood drawn steadily through a cuvette oximeter while the catheter is being withdrawn from the pulmonary artery to the superior vena cava may disclose a transient rise in saturation at the site of a small left-to-right shunt in the ventricle or atrium.

Finally, nitrous oxide inhalation may be useful.[6] If a patient breathes a gas mixture containing nitrous oxide, the content of venous blood in the right heart will remain less than that of arterial blood until blood containing nitrous oxide has passed through the arterial circulation back to the right heart. If a left-to-right shunt is present, the concentration of nitrous oxide in the chamber receiving the shunt will increase before a complete circulation has occurred. Therefore, 15 per cent nitrous oxide is breathed and integrated samples obtained simultaneously during the first minute from a peripheral artery, the chamber in which a left-to-right shunt is suspected and the chamber proximal to it via a double lumen catheter. If such a shunt is present, the sample from the

velop in these patients must again be emphasized. For example, a patient with an atrial septal defect with a large left-to-right shunt without pulmonary hypertension (4a) may gradually develop moderate (7a) then severe (12a) pulmonary hypertension with reversal of the shunt and the development of cyanosis

valvular than of the *infundibular type*, the outflow resistance presented to the right atrium is increased because of the presence of right ventricular hypertrophy or the end-diastolic pressure in the right ventricle may become elevated due to myocardial failure. If either an atrial septal defect or a patent foramen ovale is present, blood may shunt from right to left.

In patients with pulmonic stenosis and ventricular septal defect, the outflow resistance to the right ventricle resulting from the stenosis is not uncommonly of sufficient magnitude to cause an elevation of right ventricular pressure which becomes at least equal to left ventricular pressure Blood will then shunt predominantly *from right to left* through the defect. The pulmonic stenosis is most commonly of the infundibular type and the ventricular septal defect is in the membranous portion of the ventricular septum near the aortic valve If the aortic root is dextropositioned and overrides the ventricular septum, the syndrome is called the tetralogy of Fallot, but the severity of the pulmonic stenosis and the size of the ventricular defect determine the *syndrome produced* regardless of whether or not anatomic overriding is present. In some infants and very young children in this category pulmonic atresia may be present, in these instances a concavity in the P.A. roentgenogram is present in the region of the pulmonary artery.

Group 15

The final category includes patients with pulmonary hypotension and abnormal relationship of the great vessels Patients with truncus arteriosus (*a*) may uncommonly be in this group when the pulmonary arteries are small and underdeveloped The radiographic appearance is characterized by a concavity in the left upper border in the region of the pulmonary artery and a widened mediastinal shadow (FIG 13). A few individuals with complete transposition of the great vessels and pulmonic stenosis may also appear to have pulmonary hypotension and clear lung fields. In both truncus arteriosus and transposition with pulmonic stenosis, the second sound at the base of the heart is remarkably pure in tone.

SYNDROMES ACCOMPANYING A CONGENITAL CARDIOVASCULAR ABNORMALITY

The clinical syndromes which may accompany the various congenital anatomic defects of the circulation may be approached in the conventional manner by reversing the order of the flow sheet presented in TABLE 1. In the following outline, the various lesions are grouped according to the circulatory abnormality produced, as they were in FIGURE 2. The number following each refers to the group classification developed in the table

I Pressure loads	
pulmonic stenosis	*5a*
pulmonary hypertension	*12a*
coarctation of aorta	*1b*
aortic stenosis	*1a*
II Volume loads	
ventricular septal defect	*3b*
atrial septal defect	*3a, 4a and 4b*
aberrant pulmonary veins	*4a*
patent ductus arteriosus	*2a, 3c*
aortic sinus aneurysm	*2b*
aortic septal defect	*2c*
mitral regurgitation	*4b*
tricuspid regurgitation (Ebstein's)	*11a*
III Physiologic single ventricle	*13a–d, 14b, 15a and b*
transpositions of great vessels	
truncus arteriosus	

IV Combinations: In the presence of combined lesions a spectrum of clinical syndromes may occur reflecting the relative physiologic severity of the basic abnormalities forming the combination

pulmonic stenosis + ventricular septal defect	*6b, 14b*
pulmonic stenosis + atrial septal defect	*6a, 14a*
atrial septal defect	
+ moderate pulmonary hypertension*	*7a*
+ severe pulmonary hypertension*	*12a*
ventricular septal defect	
+ moderate pulmonary hypertension*	*7b*
+ severe pulmonary hypertension*	*12b*
patent ductus arteriosus	
+ moderate pulmonary hypertension*	*7c*
+ severe pulmonary hypertension*	*8b*

* The progressive nature sometimes of the acquired type of pulmonary vascular disease which may de-

dilution curves for this purpose We have found the most useful substance for these tests to be indocyanine green dye (Cardio-Green) which has a maximum light absorption at 800 angstroms and hence is not influenced by variations in oxygen saturation. To perform this test, light transmission to an ear oximeter filtered at 800 millimicrons is constantly recorded as the indocyanine green dye is injected first in the pulmonary artery, then into the right ventricle and then into the right atrium. In the absence of a shunt, the appearance time of the substance at the ear, denoted by a sharp deflection of the recording galvanometer, will register the time of circulation from the site of injection through the pulmonary circulation to the left heart, aorta and to the ear. In the presence of a communication between the right and left sides of the heart, with right-to-left shunting of blood, some of the indicator will bypass the pulmonary circulation and arrive at the ear considerably earlier than the remainder of the material which takes the longer route via the pulmonary circulation Thus, an early appearance time will be found on the curve recorded from the chamber from which the shunt occurs and all chambers proximal to the shunt. Evans blue dye (T-1824) and radioactive isotopes such as I^{131} or Chromium[51] may also be used with appropriate detectors.

In FIGURE 14, the methods commonly used for calculation of blood flows and shunts utilizing the direct Fick principle are shown.

Mixed venous blood Cv_{O_2} is the oxygen content of the blood in the chamber proximal to a shunt. In an atrial septal defect, mixed venous blood is assumed to be the sum of superior vena caval plus 2 times inferior vena caval oxygen contents divided by 3; in ventricular septal defect when blood samples from both vena cavae are available Cv_{O_2} should be calculated in this manner, but if only one caval sample is available right atrial oxygen content is used for Cv_{O_2}. When a patent ductus arteriosus is present, the oxygen content in the right ventricle should be used for Cv_{O_2}. The oxygen content of blood in the pulmonary artery Cpa_{O_2} may be measured directly. The oxygen content of pulmonary venous blood, which is ordinarily not directly measurable unless a catheter is

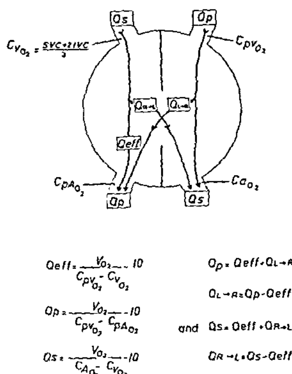


FIG 14 —The calculation of pulmonary, effective pulmonary and systemic blood flows and of shunts Qs = systemic blood flow, Qp = pulmonary blood flow, Qeff = effective pulmonary blood flow, Q R-L = right to left shunt, Q L-R = left to right shunt (L /min) V_{O_2} = oxygen consumption (ml /min) Ca_{O_2}, Cv_{O_2}, Cpv_{O_2}, CpA_{O_2} = oxygen content (ml /100 ml blood) of systemic arterial, mixed venous, pulmonary venous and pulmonary arterial blood, respectively

passed into an aberrant pulmonary vein or into a pulmonary vein from the left atrium, is calculated with an assumption of 96 per cent saturation. The oxygen content of a systemic artery Ca_{O_2} may be measured directly. If multiple manometric analyses are not available, oxygen contents may be estimated from well calibrated cuvette oximeter saturation readings by multiplying hemoglobin oxygen capacity as determined by manometric analysis on any single sample of blood from the patient by the saturation determined from the oximeter calibration curve and adding an appropriate value for dissolved oxygen content At body temperature, the factor is 003 ml. O_2/100 ml. of blood/ml. P_{O_2}. From the hemoglobin oxygen dissociation curve relating blood P_{O_2} to per cent saturation, a factor of 0.1 volume per cent for dissolved oxygen is used for 40 to 75 per

chamber proximal to the shunt will usually contain less than 1.0 volume per cent of nitrous oxide while the chamber containing the shunt and all distal to it will usually have more than 1.5 volumes per cent of the gas The arterial sample ordinarily will contain about 3 0 volumes per cent Radioactive krypton may also be used.[8]

Angiocardiography by peripheral venous injection is of little value in the diagnosis of left-to-right shunts, although occasionally definite blanching of the bolus of contrast medium will be seen as it is displaced by blood shunting from left-to-right not containing the contrast material Selective angiocardiography may demonstrate a shunt either by blanching in a chamber distal to the injection or by the forced passage of a small amount of contrast medium from right to left through a defect. In ventricular septal defect, this will usually occur only if the systolic pressure in the right ventricle is greater than 50 to 60 mm. Hg and if 8 or preferably 12 exposures per second are taken, since any right-to-left shunt is of very short duration

A left-to-right shunt into either vena cava is found with aberrant insertion of one or more pulmonary veins. A shunt into the right atrium occurs with an atrial septal defect and/or aberrant insertion of pulmonary veins; rarely, a sinus of Valsalva may communicate with the right atrium. In the presence of considerable tricuspid regurgitation, oxygenation of right atrial blood will occasionally be encountered near the tricuspid valve In the right ventricle, a left-to-right shunt is commonly through a ventricular septal defect or rarely via a communication of a ruptured sinus of Valsalva or a coronary arteriovenous fistula with the right ventricle A left-to-right shunt into the pulmonary artery is found in the presence of a patent ductus arteriousus or an aortic septal defect.

Positive differential diagnosis in the presence of arterialization of blood in these areas may be made by catheter passage through the various defects or into aberrant pulmonary veins and should be attempted diligently. If passage of the catheter through a defect is not possible, the differential diagnosis between atrial septal defect and aberrant pulmonary veins may frequently be made on the basis of the slight arterial unsaturation which commonly occurs especially during exercise in atrial septal defect. The differential diagnosis of ventricular arterialization usually may readily be made on the basis of the clinical findings of the characteristic murmur of ventricular septal defect or the continuous murmur and widened pulse pressure of a sinus of Valsalva communication The differential diagnosis between a patent ductus arteriosus and an aortic septal defect in the presence of arterialization of the pulmonary arterial blood is sometimes extraordinarily difficult and often may be made only at surgery, by a retrograde arteriogram from the left brachial artery or by injection of contrast medium through a catheter passed to the ascending aorta from the brachial artery

The presence of a right-to-left shunt may be suspected when significant unsaturation of systemic arterial blood is found In atrial septal defect, a small right-to-left shunt commonly accompanies even a large left-to-right shunt, and arterial unsaturation may be brought out by exercise or a Valsalva maneuver if not found at rest In the presence of a ventricular septal defect, a patent ductus arterious or an aortic septal defect, there may be no arterialization of blood obtained from the right heart in the presence of marked right-to-left shunting. i e, in the presence of marked arterial unsaturation; in these patients, pulmonary arterial and right ventricular pressures are commonly equal to aortic pressure The location of the shunt may sometimes become apparent by the development of a slight left-to-right shunt into the chamber with the defect during the inhalation of 100 per cent oxygen because of a decrease in pulmonary vascular resistance and a consequent lowering of pulmonary arterial pressure We have found it useful to record the saturation of blood withdrawn at constant rate through the catheter and an oximeter cuvette while the patient inhales 100 per cent oxygen as the catheter is slowly withdrawn from the pulmonary artery to the right atrium. If no arterialization of blood is found, i e , if the location of a communication between the systemic and pulmonary circulations is not located by these maneuvers, it is necessary to use indicator

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Acquired Valvular Heart Disease

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HEMODYNAMIC study technics making use of cardiac catheterization, indicator-dilution curves and the study of pressure-pulse contours have made it possible to diagnose accurately or to substantiate the diagnosis of specific, acquired valvular deformities in the human patient. By correlating data obtained by these methods with the clinical features in many typical patients, it is now possible to predict with considerable accuracy the nature of the valvular defect without the need for special physiologic studies. In spite of the accuracy inherent in hemodynamic study of patients, there remain hiatuses in a full appraisal of cardiac efficiency or reserve due to inability to estimate accurately the myocardial weakness related to such features as residua of rheumatic myocarditis or the presence of coronary insufficiency.

Although the future may reveal the application of open cardiotomy with the use of extracorporeal circulation for the surgical correction of all types of acquired valvular disease, accurate preoperative diagnosis has not, and should not, surrender to exploratory cardiotomy for all patients with a murmur and symptoms of reduced cardiac functional ability. Whereas the typical patient who has predominantly one type of defect in one valve can now be appraised with accuracy by means of conventional clinical methods, the patient who has evidence of either multivalvular deformity or multiple deforming deficits of one valve continues to be a candidate for careful, and sometimes extensive, physiologic study in the cardiac catheterization laboratory.

Application of Hemodynamic Methods

Catheterization of the right side of the heart by standard technics in patients with acquired valvular disease supplies data including pressures and oxygen content of blood samples from the great veins, right atrium and ventricle and also the pulmonary artery. Advancing the catheter to the pulmonary artery "wedge" position permits recording of a pressure pulse which has been found to correlate well with similar determinations recorded from the left atrium. Pressure gradients recorded in the appropriate phase of the cardiac cycle on withdrawal of the catheter through the pulmonary and tricuspid valves will indicate the presence or absence of stenosis of these valves. Cardiac output is determined by the Fick principle at the time of right heart catheterization by simultaneously sampling blood from a systemic artery and the pulmonary artery at a time when oxygen consumption is being recorded. Right heart catheterization provides data on pressure and flow that permit the calculation of the total and arteriolar pulmonary resistance and also mitral valve area through the application of appropriate equations[17, 23] Unfortunately, right heart catheterization leaves much to be desired in a complete appraisal of deformity of the valves of the left side of the heart. Abnormalities apparent in data on the right heart chambers and pulmonary arteries reflect the consequences of mitral and aortic valvular defects, but the defects are not accurately differentiated.

The procedure of catheterization of the left side of the heart was developed with the hope that simultaneous measurement of pressures in the left atrium, left ventricle and aorta, together with determination of the cardiac output, would permit accurate assessment of abnormalities of the mitral and aortic valves. The three more commonly used procedures for left heart catheterization are the posterior percutaneous, the transbronchial and the suprasternal percutaneous technics.[6, 11, 15, 29] The

cent saturation, from 75 to 85 per cent saturation 0 2 volumes per cent and over 85 per cent saturation 0 3 volume per cent, therefore, in calculating pulmonary venous content, a factor of 0 3 volume per cent is added to the calculated hemoglobin oxygen content to obtain an approximation of total oxygen content

Inspection of the diagram will make clear that pulmonary flow consists of a portion of the systemic return flow which will be oxygenated in the lungs plus any blood which has shunted from left to right through a defect Since this latter component is fully oxygenated, oxygen consumption in the lungs will be accounted for entirely by the venous blood in the total pulmonary flow which is called the effective pulmonary flow.

The concentration of oxygen in the pulmonary artery Cpa_{O_2} will be the resultant of the mixture of the oxygen concentration of the effective pulmonary flow and the oxygen concentration of the blood shunting from left to right Similarly, it can be seen that systemic blood flow may consist of two portions, namely, blood which is returned from the pulmonary veins and any venous blood returning from the systemic circuit which has shunted from right to left through a defect. The concentration of oxygen in the aorta Ca_{O_2} will thus be determined by the concentration of oxygen in pulmonary venous blood and any systemic venous blood which has joined the systemic flow without passing through the lungs

Since the oxygen consumed in the lungs is carried by the effective pulmonary flow, the effective pulmonary flow may be calculated by oxygen consumption divided by the arteriovenous oxygen difference between pulmonary venous and systemic venous blood Total pulmonary flow may be calculated by dividing oxygen consumption by the arteriovenous oxygen difference of pulmonary venous and pulmonary arterial blood and systemic blood flow by dividing oxygen consumption by the arteriovenous difference of systemic arterial and systemic venous blood. Since pulmonary flow consists of effective flow plus left-to-right shunt flow, the left-to-right shunt may be obtained by subtraction Similarly, since systemic flow consists of effective pulmonary flow plus right-to-left shunt, the right-to-left shunt may be obtained by subtraction The over-all shunt or net shunt will be the difference between systemic and pulmonary flow. In performing these calculations, it must be recognized that shunts are often variable from moment to moment and that the smaller the arteriovenous difference the greater possibility of error in the calculations.

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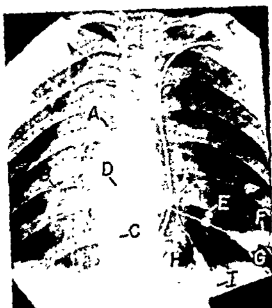


FIG 2 —Antero-posterior view of thorax during simultaneous catheterization of right heart, aorta and left heart. The tip of the catheter (A) (inserted via right arm) is in the pulmonary artery The tip of the arterial catheter (C) (inserted via the right femoral artery) is in the descending aorta The tip of the left atrial needle (D) (inserted from the right dorsal surface of the thorax, marked by needle stop (E)) is in the left atrium The tip of the catheter (B) in the left side of the heart lies in the left ventricle Left atrial pressure is recorded via the lead tubing (F) [illegible]

catheter passes through this assembly and is connected by a hypodermic adaptor (H) to a second lead tube (I) for recording of left ventricular pressure (See FIGURE 1 for further details) The patient's right side is on right side of roentgenogram

monary artery and aorta permit determination of cardiac output The third part of this procedure is the accomplishment of a left atrial puncture performed under fluoroscopic control A long needle is introduced into the right posterior portion of the thorax, in the interspace providing the most direct route, until the left atrium is entered A small catheter may then be introduced through this needle and advanced into the left ventricle Since pressures may be obtained simultaneously from the catheter in the left ventricle, through the needle in the left atrium and through the catheter in the aorta, measurements are made which give information concerning pressure gradients across both the mitral and the aortic valves By this means it is possible to determine the presence or absence of stenosis of these valves, and, in the absence of regurgitation, to determine the size of the orifices of the valves.

Indicator-dilution methods also have been found to be of value in studying the altered hemodynamics resulting from acquired valvular heart disease When an indicator dye is injected suddenly into the circulatory system, it is mixed with and transported by the blood throughout the body in a characteristic manner [24] A record of its concentration against time during the initial traversal of the circulation is called an "indicator-dilution curve." This technic is described in detail in Chapters 9 and 23 FIGURE 3 shows examples of such dilution curves obtained in a patient before and after mitral commissurotomy

The more commonly used indicators include dyes such as Evans blue (T-1824) and the recently introduced tricarbocyanine dye II (Cardio-Green dye)[16], less commonly used are the radio-active materials such as radiopotassium.[8]

The ability to obtain samples from, and to inject directly into, the left heart chambers during left heart catheterization permits an even wider application of dye-dilution methods in studying valvular heart disease [21] For example, dye may be injected into the left ventricle with sampling from the left atrium. The presence of early appearing dye in the resulting curve would indicate the presence of mitral regurgitation

ACQUIRED MITRAL VALVULAR DISEASE

The etiology of acquired mitral valvular disease can be said to be due principally to rheumatic fever Occasionally, severe mitral regurgitation will evolve from destructive changes in a hitherto essentially normal valve as the result of subacute bacterial endocarditis, and, rarely, similar valvular dysfunction will be produced by the rupture of an infarcted papillary muscle or chordae tendineae cordis secondary to occlusive coronary artery disease or to trauma. A tightly stenotic valve with secondary pulmonary hypertension has been found to develop as soon as two years after

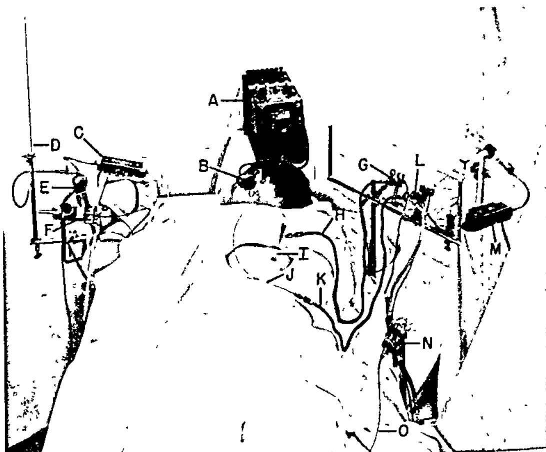


FIG 1 —Assembly of instruments used during performance of simultaneous catheterization of right side of heart, aorta and left side of heart Twin-tube oscilloscope (A) with long-persistence screen for continuous monitoring of the electrocardiogram and the pressure being transmitted via the catheter in the left heart (J) Ear oximeter (B), cuvette oximeter (C) connected to indwelling needle in radial artery and to a P-6 Statham strain-gauge manometer (E) Burette (D) for measuring rate of blood flow through cuvette oximeter during recording of dye-dilution curves Strain-gauge manometer (F) connected to cardiac catheter inserted percutaneously, via a needle in an antecubital vein, and advanced so that its tip lies in the pulmonary artery P23G strain-gauge manometer (G) connected to lead tubing (H) for recording of left atrial pressure via lumen between shaft of 19T gauge needle (I) and catheter in the left ventricle (J) Lead tubing (K) connects catheter in left ventricle to a P23D strain-gauge manometer (L) for recording of left ventricular pressure Cuvette oximeter is used (1) to verify position of tip of needle in left atrium by determining that blood withdrawn from the needle ... after

catheter (O) inserted percutaneously via a 19T gauge needle in the right femoral artery.

last-mentioned technic is employed occasionally in conjunction with direct percutaneous puncture of the left ventricle (the Brock procedure).[6] In the complete study using the posterior percutaneous technic, three separate catheterization procedures are done[33] (FIGS 1 AND 2) First, right heart catheterization is accomplished by the usual technic, and the described measurements are made. The catheter tip is left in the pulmonary artery during the remaining procedure Second, an arterial catheter is introduced through a needle in a femoral artery and is advanced into the descending aorta Through this catheter, central arterial pressures and pulse contours may be obtained. Simultaneous samples of blood obtained from the pul-

for the various symptoms and clinical course noted in patients with mitral stenosis. Supported by confirmatory studies from other laboratories, the hemodynamic consequences of mitral stenosis are most clearly described by Dexter and associates.[11,25] When the normal mitral valve orifice, which measures 4 to 6 cm.[2] and which requires only a diastolic atrioventricular pressure gradient of 1 to 2 mm. Hg to maintain a normal cardiac output, is narrowed by disease, the clinical syndrome develops. Although a characteristic murmur is present, mild degrees of mitral stenosis in which the valve orifice is 2 to 2.5 cm.[25] do not produce symptoms since the first compensatory mechanisms are slight reductions of cardiac output at rest with or without the elevation of the left atrial pressure within reasonable limits to maintain a normal flow.

Since pulmonary capillary, pulmonary vein and left atrial pressures are the same, increases in left atrial pressure to maintain flow through the stenotic valve result in similar elevation of pressure in the pulmonary vein and pulmonary capillary. The limit to which pulmonary capillary pressure may rise before producing symptoms is dependent on the osmotic pressure of plasma which is in the neighborhood of 25 to 30 mm. Hg. Intracapillary pressure much in excess of this level results in transudation of fluid into the parenchyma of the lungs producing dyspnea and pulmonary edema. Mild mitral stenosis thus can be tolerated without symptoms if the left atrial pressure increase needed to maintain adequate cardiac output remains below the plasma osmotic pressure.

Symptoms of effort dyspnea will occur when left atrial pressure must be increased to that of the plasma osmotic pressure to produce the increased flow demanded as a result of exercise. When the stenosis is increased, a point is reached at which, even at rest, the left atrial pressure, and therefore the pulmonary capillary pressure, must approach 25 to 30 mm. Hg to maintain normal blood flow. At this "critical" degree of mitral stenosis, which has been measured as being 1 cm.[2] or smaller, the symptoms of severe or tight mitral stenosis become manifest. The symptoms produced at this level will depend on another compensatory mechanism which is the development of varied degrees of pulmonary arteriolar resistance. Pulmonary arteriolar resistance due to functional or organic changes in the pulmonary arterioles and small pulmonary arteries increases apparently as a consequence of high pulmonary capillary pressures.

Physiologically, the development of increased pulmonary vascular resistance seems to lower cardiac output and to protect the pulmonary capillaries from increased discharge of blood into them from the right ventricle. This same elevation of pulmonary vascular resistance, however, results in pulmonary arterial hypertension and thereby increases the work load of the right ventricle. The inevitable result of severe pulmonary hypertension is right ventricular hypertrophy and, ultimately, congestive heart failure.

Roentgenologic and Electrocardiographic Findings

The patient with mitral stenosis usually will display a characteristic cardiac silhouette. In the postero-anterior projection, convexities will appear on the left border of the cardiac silhouette which are respectively from cephalad to caudad, a small aortic knob, a pulmonary artery prominence, the left auricular appendage which widens the waist of the heart and then the cardiac apex made up of either a small portion of the left ventricle or, in the case of severe mitral stenosis, the hypertrophied right ventricle. In many cases, such as in FIGURE 4, the enlarged left atrium can be visualized as forming a double contour within the cardiac shadow and as presenting near the right cardiac border.

The presence of multivalvular lesions will detract from the rather clear-cut diagnostic x-ray features of mitral stenosis by producing enlargement of additional cardiac chambers. A helpful and useful roentgenologic finding seen in patients with pulmonary venous hypertension and primarily in those with severe mitral stenosis is the presence of costophrenic septal lines[7] (FIG. 5). With suitable roentgenologic technic, calcification of the mitral valve will be seen when it is present. When there has been long-standing chronic left atrial failure, pul-

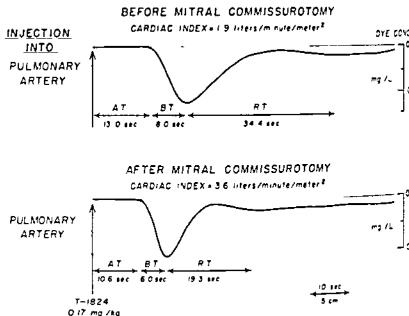


FIG 3 —Changes in dilution curves associated with congestive heart failure in a 41 year old man with mitral stenosis The dilution curve in the upper panel was recorded before and that in the lower panel six months after mitral commissurotomy Before relief of mitral stenosis, the cardiac index was below the range of normal, after commissurotomy, a normal value was obtained The lower curve is of normal contour and the time components (A T = appearance time, B T = build-up time, R T = systemic recirculation time) are within the range of normal values A feature of the upper curve is the prolongation of the time components seen in patients with reduced cardiac output In particular, note the dramatic changes in recirculation time (R T) from 34 4 seconds before operation to 19 3 seconds after operation

acute rheumatic fever in some patients, in others with mitral valvular lesions, significant obstruction will not develop in a normal lifetime

Mitral Stenosis

Clinical Syndrome

A well documented history of rheumatic fever can be obtained from somewhat more than half of the patients with mitral stenosis The typical story obtained from a patient with well advanced mitral stenosis syndrome is that of progressively decreasing exercise tolerance owing to dyspnea with physical exertion and to easy fatigability. The course may be punctuated with alarming episodes of acute paroxysmal dyspnea or hemoptysis. Initially intermittent cardiac arrhythmia will usually become permanent. Evidence of right ventricular failure gradually develops with peripheral edema and abdominal enlargement As the result of left atrial enlargement and cardiac arrhythmia, left atrial thrombosis is likely to occur and may produce peripheral systemic embolization.

Physical examination supplies diagnostic criteria in the usual patient with mitral stenosis of moderate severity. Most characteristic and diagnostic of the auscultatory phenomena is a relatively low-pitched and rumbling mid-diastolic apical murmur which is followed by a crescendo presystolic component, if the cardiac rhythm is of a sinus mechanism The diastolic murmur is heard well into the left axilla and may be accompanied by a palpable thrill. Its intensity is increased when the patient lies on his left side. The first heart sound is characteristically loud and snapping, and the second heart sound, when heard over the pulmonic valve area, is accentuated Frequently, an additional sharp sound can be heard in early diastole, it occurs simultaneously with opening of the mitral valve and has been called the "opening snap of the mitral valve." When pulmonary hypertension has produced dilatation of the pulmonary trunk, there frequently occurs the soft blowing diastolic murmur of pulmonic regurgitation which is the Graham Steell murmur. When congestive failure has occurred, there will be various gradations of peripheral edema, hepatomegaly and evidence of pulmonary congestion or pleural effusion

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A firm physiologic explanation based on careful hemodynamic studies has been attained

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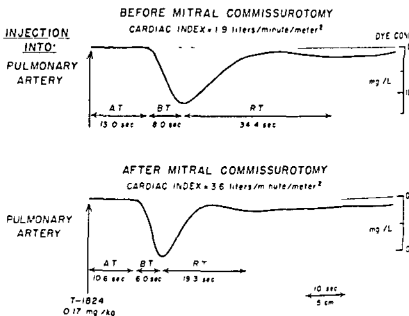


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Pathologic Physiology

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FIG 5—X-rays of the lower right and left lung fields of two patients with mitral stenosis which illustrate costophrenic septal (horizontal) lines

r hypertrophy in an additional 19 cases, ght bundle-branch block was present in six. lectrocardiography is a valuable adjunct in ie diagnostic profile for mitral stenosis, but it iay not be diagnostic in borderline situations.

MITRAL REGURGITATION

Clinical Syndrome

Mitral regurgitation in the pure chronic form is a consequence of rheumatic fever occurs less frequently than mitral stenosis, and usually even when mitral regurgitation is the dominant hemodynamic abnormality, some degree of mitral stenosis coexists Mitral regurgitation may result from changes of the valve secondary to subacute bacterial endocarditis.

There are no characteristic symptoms attributable to mitral regurgitation of mild degree The course of patients with relatively pure mitral regurgitation due to rheumatic fever is said to be benign, and chronic disability is delayed until the fifth or sixth decade. Generally, the patient with mitral regurgitation experiences easy fatigability and weakness which is out of proportion to dyspnea on physical exertion With the onset of left ventricular failure, dyspnea and orthopnea will develop and will be followed by evidence of right heart failure The incidence of arterial embolization has been found to be lower when mitral regurgitation predominates than when mitral stenosis is present. Chronic atrial fibrillation is frequently associated with mitral regurgitation.

The classic physical finding in mitral regurgitation is the presence of a significant blowing or harsh systolic murmur, which is loudest at the cardiac apex and also is heard well in the left axilla and the back. On occasion, a palpable thrill accompanies the murmur, but this occurs much less frequently than a diastolic thrill with mitral stenosis In contrast to central precordial heaving of mitral stenosis, a palpable or visible apical thrust of left ventricular enlargement ac-

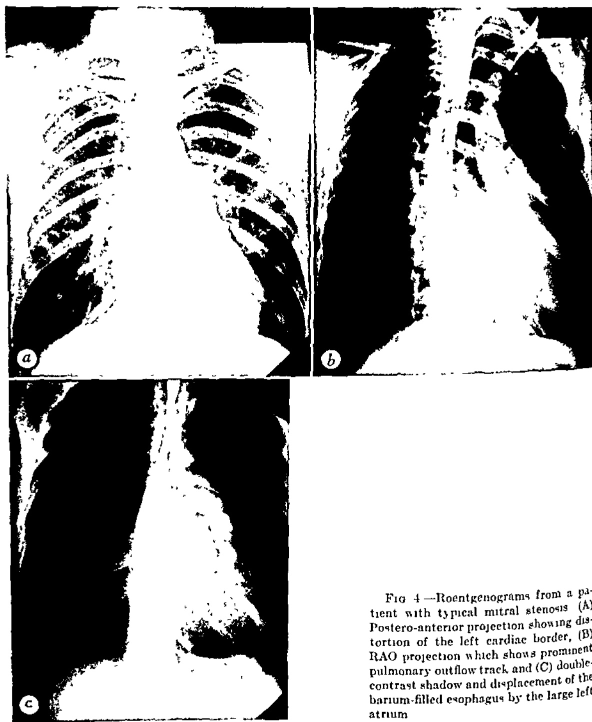


FIG 4 —Roentgenograms from a patient with typical mitral stenosis (A) Postero-anterior projection showing distortion of the left cardiac border, (B) RAO projection which shows prominent pulmonary outflow track and (C) double-contrast shadow and displacement of the barium-filled esophagus by the large left atrium

monary hemosiderosis manifested as miliary infiltration of the parenchyma of the lung may be present.

Electrocardiographic examination is helpful but not diagnostic for mitral stenosis The electrocardiogram will reflect the presence of left atrial and right ventricular enlargement in the presence of tight mitral stenosis. When there is a sinus rhythm, the P waves in standard leads I and II are broadened and those of the right precordial leads may be of high amplitude or diphasic as a reflection of atrial enlargement Atrial fibrillation is a frequent accompaniment of mitral stenosis. Right ventricular hypertrophy occurring in 41 of 92 surgically proved cases of mitral stenosis was found by Pruitt and associates,[29] and the electrocardiogram was suggestive of right ventricu-

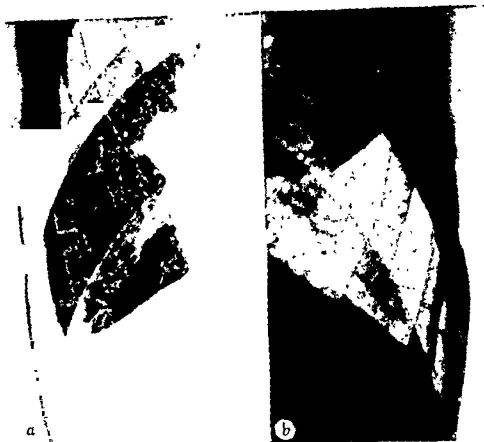


FIG 5 —X-rays of the lower right and left lung fields of two patients with mitral stenosis which illustrate costophrenic septal (horizontal) lines

lar hypertrophy in an additional 19 cases, right bundle-branch block was present in six Electrocardiography is a valuable adjunct in the diagnostic profile for mitral stenosis, but it may not be diagnostic in borderline situations

MITRAL REGURGITATION

Clinical Syndrome

Mitral regurgitation in the pure chronic form as a consequence of rheumatic fever occurs less frequently than mitral stenosis, and usually even when mitral regurgitation is the dominant hemodynamic abnormality, some degree of mitral stenosis coexists Mitral regurgitation may result from changes of the valve secondary to subacute bacterial endocarditis

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companies mitral regurgitation Ordinarily, the systolic murmur begins early and reduces the loudness of the first heart sound. The second heart sound in the pulmonic valve area may be accentuated if pulmonary hypertension has developed.

Pathologic Physiology of Mitral Regurgitation

Hemodynamic studies in patients with predominant mitral regurgitation reveal that this lesion cannot be distinguished with certainty from mitral stenosis by means of right heart catheterization An incompetent mitral valve during ventricular systole increases left ventricular work in order to maintain an adequate cardiac output through the aorta in the presence of significant regurgitation of blood into the left atrium[18] If mitral regurgitation is minimal, aortic output will be kept normal by virtue of the increase in left ventricular work without the production of symptoms. The characteristic result of hemodynamically significant mitral regurgitation, however, is a decrease in aortic output. By virtue of the systolic ejection of blood into the left atrium, pressure in that chamber is elevated, and, in particular, the left atrial V wave is heightened Similar to the situation which pertains in mitral stenosis, the left atrial pressure is reflected in the pulmonary capillary pressure where increased pressure is associated with increased pulmonary arteriolar resistance and pulmonary hypertension When left ventricular failure results and is associated with increased left ventricular diastolic pressure, left atrial pressure must increase to insure diastolic filling of the left ventricle. This phase is associated with further increased pressure in the pulmonary capillary and the pulmonary artery, the consequence is pulmonary congestion, increased right ventricular work and, finally, both right and left cardiac failure.

Roentgenologic and Electrocardiographic Findings

Mitral regurgitation, in addition to producing left atrial and ultimate right ventricular enlargement, as is true in mitral stenosis, also causes left ventricular enlargement, which frequently can be demonstrated on x-ray exami-

dilatation of the left atrium, occasionally seen in patients with mitral valvular disease, is most often associated when mitral regurgitation is the predominant lesion. Unfortunately, this readily detectable finding is not diagnostic, since severe mitral stenosis occasionally may cause a giant left atrium, and mitral regurgitation may be severe in the absence of such an atrium

The pertinent electrocardiographic abnormality of mitral regurgitation which is in direct contrast to mitral stenosis is the added evidence of left ventricular hypertrophy. Pruitt and co-workers[29] detected left ventricular hypertrophy in 72.7 per cent of 22 patients with surgically proved mitral regurgitation, but they also noted that in 9.1 per cent of this same group the pattern of right ventricular hypertrophy was evident While the electrocardiogram is a useful aid and at times may be sufficiently definite to determine clearly that predominant mitral regurgitation exists, the presence of a ventricular hypertrophy pattern of either type may accompany both hemodynamically significant mitral stenosis and mitral regurgitation

Hemodynamic Data in Acquired Deformity of the Mitral Valve

The principal abnormalities detected by right heart catheterization in patients with predominant mitral stenosis include elevated pulmonary artery and pulmonary artery wedge pressures, a decrease in cardiac output and an increase in pulmonary arteriolar and total pulmonary resistance When the patient with mitral stenosis exercises, his cardiac output does not increase normally, the result is abnormal increases in pressures in the pulmonary circulation and in pulmonary resistance when contrasted with those of normal persons. These hemodynamic data are illustrated in TABLE 1 When mitral stenosis is the sole lesion present, these data obtained from right heart catheterization will aid the cardiologist and the cardiac surgeon in determining the advisability of recommending surgical treatment.

The hemodynamic data most often desired, however, are those which will aid in distinguishing significant mitral regurgitation when both

TABLE 1.—*Average Hemodynamic Data at Rest and with Exercise in Normal* Persons and in Patients with Mitral Stenosis, Mitral Regurgitation and Aortic Stenosis*

		Normals* 12 to 25 subjects	Mitral stenosis		Mitral regurgitation 20 cases†	Aortic stenosis 5 cases†
			18 cases‡	24 cases†		
Pressures						
Right atrial, mean (mm Hg)	rest	6 (2-10)	8.5 (2-18)	6	8	10
	exercise					
Pulmonary artery, mean (mm Hg)	rest	17 (10-22)	50 (22-84)	40 (18-72)	44 (19-78)	49 (39-59)
	exercise	24	74 (34-112)	65 (35-112)	54 (28-80)	
Pulmonary artery wedge, mean (mm Hg)	rest	12 (8-15)	27 (18-33)	24 (12-46)	23 (14-39)	35 (34-36)
	exercise		39 (23-41)	34 (23-47)	32 (21-42)	
Cardiac index (L/min/M²)	rest	3 5 (2 8-63)	2.1 (1 2-3 1)	2 6 (1 5-3 9)	2.6 (1 6-3 9)	2 6 (2 2-3.5)
	exercise	5 7	2 5 (1.3-4 0)	3 5 (1 8-5.5)	3 2 (2.0-4.1)	
Pulmonary arteriolar resistance (dyne sec cm⁻⁵)	rest	67 (44-106)	642 (241-1239)	350	200	
	exercise		828 (328-1957)	500	300	
Total pulmonary resistance (dyne sec, cm⁻⁵)	rest	189 3 (90-291)	1249 (533-2245)	750	600	
	exercise	162.1 (106-233)	1608 (566-3239)	1050	750	
Mitral valve area (cm²)			0 6 (0 4-1 3)	0 9 (0 4-1 6)		

* Adapted from Barratt-Boyes and Wood [5,6]
† Adapted from Connolly and Wood.[10]
‡ Adapted from Tompkins [31]

stenosis and regurgitation are present As indicated in the table the variables obtained from right heart catheterization are, on the average, similar in series of patients with predominant mitral regurgitation and predominant stenosis where lesions have been confirmed either at operation or necropsy

Since these data do not allow separation of patients with mitral regurgitation from those with mitral stenosis, numerous workers turned to analysis of the pulmonary artery "wedge" pulse contour in an attempt to find a quantitative measurement that would clearly distinguish mitral stenosis from mitral regurgitation. Considerable evidence has been presented indicating that the pulmonary artery wedge pressure, in most instances, corresponds closely to the left atrial pressure in both magnitude and contour.[5]

Since the regurgitant or V wave occurs during ventricular systole, most workers have confined their attention to the systolic portion of the "wedge" pressure pulse Attempts to utilize the magnitude of the V wave alone as a means of differentiating mitral stenosis from mitral regurgitation have not been uniformly successful.[26]

Connolly and Wood[10] did find close correlation between the average peak pressure of V waves and the mean wedge pressure in cases of pure mitral stenosis At equivalent increases of mean pulmonary artery wedge pressure, the peak V wave pressure was significantly greater in patients with mitral regurgitation than it was in patients with mitral stenosis (FIG. 6) When the mean pulmonary artery wedge pressure exceeded 20 mm Hg, no overlap was encountered in the relationship of the peak V wave pressure to the mean wedge pressure in their series of patients with severe mitral regurgitation and pure mitral stenosis.

Inability to obtain uniform differentiation of patients with predominant regurgitation from those with predominant stenosis on the basis of

companies mitral regurgitation. Ordinarily, the systolic murmur begins early and reduces the loudness of the first heart sound. The second heart sound in the pulmonic valve area may be accentuated if pulmonary hypertension has developed

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Mitral regurgitation, in addition to producing left atrial and ultimate right ventricular enlargement, as is true in mitral stenosis, also causes left ventricular enlargement, which frequently can be demonstrated on x-ray examination. Unusual enlargement or aneurysmal dilatation of the left atrium, occasionally seen in patients with mitral valvular disease, is most often associated when mitral regurgitation is the predominant lesion. Unfortunately, this readily detectable finding is not diagnostic, since severe mitral stenosis occasionally may cause a giant left atrium, and mitral regurgitation may be severe in the absence of such an atrium

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pulmonary artery wedge pressure pulse led to the development of methods for puncture of the left atrium in human beings with the chief objective in mind that direct recordings of left atrial pressure would make possible this differentiation with certainty. By measurement of the diastolic pressure gradient across the mitral valve along with blood flow, it has been demonstrated that pure mitral stenosis can be detected and quantitated with considerable accuracy Pure mitral regurgitation also can be demonstrated with acceptable certainty (Fig 7). It was found, however, that the magnitude of the pressure gradient across the mitral valve lost its importance when significant stenosis and regurgitation coexisted, since only the net forward flow across the valve can be measured and the actual flow during diastole is unknown

Analysis of the directly recorded left atrial pressure pulse contour has shown that somewhat better discrimination can be obtained than by the use of the pulmonary artery wedge pressure pulse, however, some overlap was still found in cases in which mitral stenosis and mitral regurgitation were coexistent.[26] The best differentiation seems to be made by comparison of the peak V wave pressure to the mean left atrial pressure (Fig. 8). Probably an important factor in failure to obtain uniform differentiation of predominant stenosis and regurgitation by analysis of the left atrial and pulmonary artery wedge pulse contours is variation in compliance of the left atrium.

A different method of assessing the degree of mitral stenosis and regurgitation is by the use of indicator-dilution curves. Figure 3 illustrates the effect of stenotic valvular disease and consequent congestive heart failure by a comparison of arterial dilution curves recorded before and after surgical relief of severe mitral stenosis The proportionate slowing of all time compo

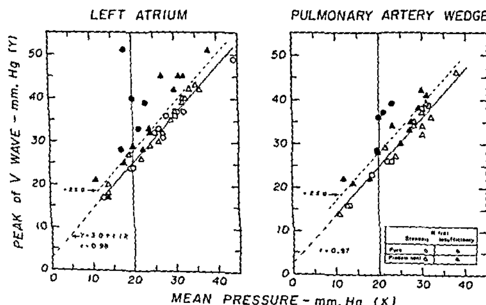


Fig 8 —Relationship between th ... pul ... ssure in pres ... t atrial wed ... artery ... were obtained in 33 of these patients The regression line for patients with "pure" and predominant mitral stenosis calculated from the directly recorded left atrial pressures is shown in both panels (*solid line*). The broken lines represent two standard deviations above the regression line Note that the same regression line fits both sets of data When the mean left atrial pressure exceeded 20 mm Hg, values in only two patients with predominant mitral regurgitation fell into the range of values found in patients with predominant mitral stenosis (From Marshall, H. W , Woodward, E Jr ,, and Wood, E. H Hemodynamic methods of differentiation of mitral stenosis and regurgitation Am J Cardiol, 2 24-60 (July) 1958)

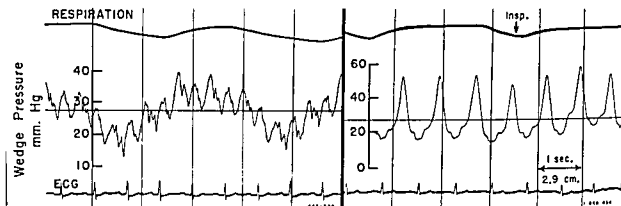


FIG 6.—Comparison of pulmonary artery wedge pressure pulse contours in a patient with mitral stenosis (*left*) and in a patient with mitral regurgitation (*right*) (each diagnosis confirmed at operation) Note that in each patient the integrated mean pulmonary artery wedge pressure was 28 mm Hg and the average heart rate was 90 per minute with normal sinus rhythm In the patient with mitral stenosis the average peak V wave measured 34 mm Hg, and in the patient with mitral regurgitation it measured 50 mm Hg. (From CONNOLLY, D C, AND WOOD, E H Hemodynamic data during rest and exercise in patients with mitral valve disease in relation to the differentiation of stenosis and insufficiency from the pulmonary artery wedge pressure pulse J Lab & Clin Med *49* 526–544 [April] 1957)

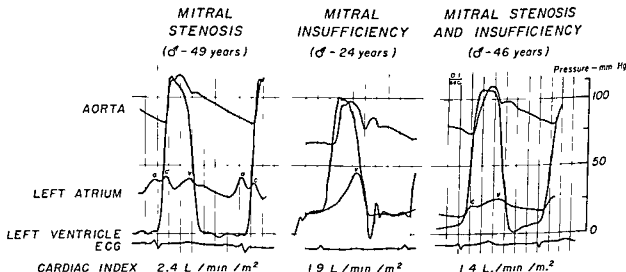


FIG 7 —Simultaneously recorded left atrial, left ventricular, and aortic pressure pulses (redrawn to identical pressure scale), showing recordings from a 49 year old man with "pure" mitral stenosis (*left panel*), a 24 year old man with "pure" mitral regurgitation (*middle panel*) and a 46 year old man with combined mitral stenosis and regurgitation (*right panel*) The [illegible] across [illegible] tion shows the typical characteristics that can be used as a basis for differentiation of patients with severe regurgitation from those with severe mitral stenosis These are as follows (1) a high peaked V wave, (2) no apparent C wave, since the trough, or X wave, between the C and V waves is absent; (3) if the C wave could be distinguished at the beginning of ventricular systole, its amplitude would be far exceeded by the V wave, (4) a rapid descent of the V wave at the termination of ventricular systole The left atrial pressure pulse in the patient with combined stenosis and regurgitation shows characteristics of both stenosis and regurgitation (From MARSHALL, H W, WOODWARD, E., JR, AND WOOD, E. H · Hemodynamic methods of differentiation of mitral stenosis and regurgitation Am J Cardiol *2* 21-60 [July] 1958)

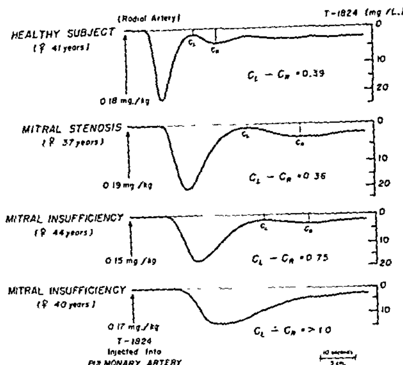


FIG. 10 Changes in contour and the points of least concentration (C_L) and systemic recirculation concentration (C_R) of dilution curves from a healthy person and three patients with mitral valvular disease. Values calculated for the ratio C_L/C_R for each curve are shown. In the curve with no detectable systemic recirculation recorded from a patient with severe mitral regurgitation, the value for the ratio C_L/C_R is designated as greater than 1.

Keys and associates[21] discussed a further application of indicator dye, and suggested that if dye is injected through the catheter into the left ventricle during left heart catheterization and is recorded immediately from the left atrial needle, mitral regurgitation must be present. Because of the incomplete mixing of dye in the left atrium, this method has been found to be of limited value.[22]

One further application of cardiac hemodynamic studies has been the postoperative evaluation of results in patients who have undergone operation on the mitral valve. General experience has indicated subjective improvement in a high percentage of patients when a stenotic mitral valve is opened. Lev and associates[24] were able to demonstrate an immediate decrease in left atrial pressure immediately after operation on the mitral valve. Similarly, they demonstrated an immediate fall in pulmonary artery pressure in 12 of 14 patients. Ellis and [illegible] con- [illegible] nody- namic variables in patients who [illegible] rgone commissurotomy in studies made approximately three weeks and one year after operation. There was good correlation between the subjective symptoms and clinical course and the objective improvement in hemodynamic data.

ACQUIRED AORTIC VALVULAR DISEASE

Acquired deformity of the aortic valve is productive of either stenosis or regurgitation or a combination of these hemodynamic abnormalities. Characteristically, deformities of the aortic valve resulting from rheumatic fever do not become clinically symptomatic until many years after the rheumatism. Since aortic stenosis, in particular, appears to evolve slowly, relatively long survival is more frequent than with associated dominant aortic regurgitation. Aortic stenosis develops insidiously on aortic valve leaflets that are deformed or otherwise disturbed by rheumatic fever in the majority of cases. The finding of bicuspid valves at necropsy, however, has been advanced as reason- [illegible] that possibly the stenotic process [illegible] valve [illegible] as the result of repeated bacterial [illegible] r as a result of trauma in the left ventricular outflow tract secondary to its deformity. When the evidence for an inflammatory background is absent either historically or pathologically in elderly people, atherosclerotic thickening, fibro-

nents of the upper curve results from the low cardiac output and the increase in blood volume associated with congestive cardiac disease.

Cardiac disease due to valvular regurgitation not only causes the changes in flow and volume associated with congestive heart failure but also produces *an abnormal flow pattern through the heart*, since both forward and backward flow occur through the incompetent valve (Fig. 9). It should be pointed out that the abnormalities of an arterial dilution curve produced by a left-to-right shunt are closely similar to those associated with severe valvular regurgitation. *Thus, the presence of a left-to-right shunt must* be ruled out before a dilution curve is analyzed in relation to regurgitant valve deformities.

When dilution curves in severe mitral stenosis are compared with those in severe mitral regurgitation, the differences associated with these two types of valvular disease are evident. However, the differences in borderline cases are not readily discernible by simple inspection. Therefore, *methods for objective quantitation* of the changes produced by valvular regurgitation have been developed.[25] The most accurate[26] of these methods and one that requires simple measurements is the ratio of the least concentration (C_L) to the recirculation concentration (C_R) (Fig. 10). In most instances, when the ratio of *least concentration to recirculation* concentration (C_L/C_R) is greater than 0.65 the predominant lesion is mitral regurgitation

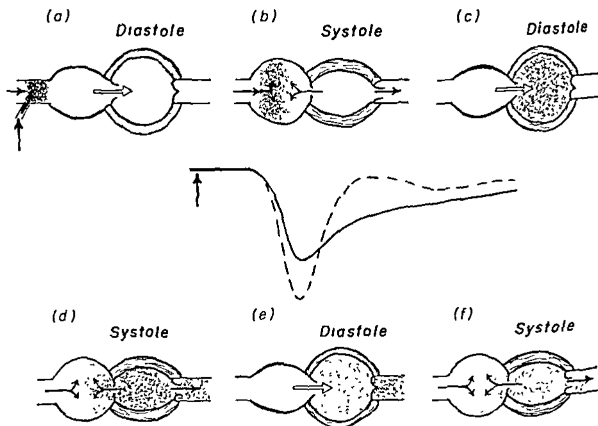


Fig. 9.—Diagrammatic illustration of the effect of valvular regurgitation on the passage of an indicator through the cardiac chambers. In the center of the figure are illustrated a normal curve (*broken line*) and the abnormal (*solid line*) dilution curves associated with severe valvular regurgitation. Indicator is injected at the inflow to the cardiac chamber (a). When it flows into the atrium during the next ventricular systole (b), it is diluted by the volume of blood regurgitated through the incompetent valve during systole. The dye-blood

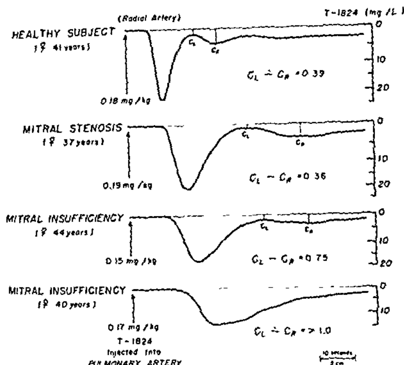


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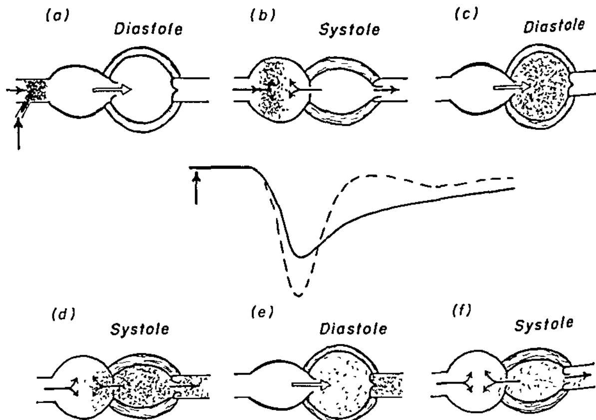
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amplitude, the build-up time is prolonged, and there is an abnormal anacrotic pause.[12] Symptomatic coronary insufficiency, although it may be due to coronary atherosclerosis, also occurs as a consequence of obstruction of the aortic valve alone. Effort syncope in patients with aortic stenosis apparently results from cerebral ischemia.

Roentgenologic and Electrocardiographic Features

X-ray and fluoroscopic examinations of the hearts of patients having aortic stenosis supply both nonspecific and diagnostic evidence related to the valvular lesion Nonspecific evidence is to be found in the presence of roentgenologic signs of left ventricular hypertrophy and enlargement. This may vary from slight to massive cardiomegaly in which the cardiac silhouette has the characteristic shape of a boot

Definitive evidence for aortic valvular deformity usually of the stenotic type comes from the demonstration of calcification in the valve area (Fig. 11). Calcified aortic valve leaflets are detected as dancing x-ray opacities at the aortic root by the fluoroscopist

The predominant electrocardiographic pattern is that of left ventricular hypertrophy. Electrocardiographic findings consistent with left ventricular hypertrophy were present in 68 per cent of a clinical series of patients who were operated on and these findings, together with left bundle branch block, occurred in 63 8 per cent of patients studied pathologically[1] Atrial fibrillation occurs in only about 10 per cent of patients having pure aortic stenosis.[27] Despite the frequent occurrence of angina pectoris with aortic stenosis, myocardial infarction with characteristic electrocardiographic findings is a distinct rarity unless there is severe coronary occlusive disease Conduction disturbances including bundle-branch block and complete A-V dissociation occur not uncommonly in aortic stenosis

Aortic Regurgitation

Clinical Syndrome

Incompetency of the aortic valve leaflets which permits regurgitation of previously expelled blood from the aorta into the left ventricle during diastole may occur as an isolated cardiac abnormality or its effects may be tempered by simultaneous aortic stenosis. When the aortic leak is minimal, it may remain merely an auscultatory finding and may not produce either symptoms or hemodynamic abnormality. A significant leak, whether secondary to inflammation or trauma, is productive of symptoms secondary to left ventricular failure. Awareness of cardiac overactivity and fatigability are frequently symptoms prior to the onset of effort dyspnea Angina pectoris and symptoms of cerebral ischemia occur less commonly than with pure aortic stenosis but still with appreciable frequency.

Examination of the patient with minimal aortic regurgitation may not reveal cardiovascular abnormality other than a short soft early decrescendo diastolic murmur, which is heard only at the left parasternal line with the patient's co-operation in leaning forward in a sitting position at full expiration The significance of such a lesion is primarily its availability as a focus for the implantation of bacterial endocarditis

In clinically significant aortic regurgitation, inspection will show the presence of prominent systolic pulsations involving the carotid arteries Capillary pulsations can be demonstrated Measurement of blood pressure reveals an abnormally high pulse pressure, with increased systolic pressure and decreased diastolic pressure contributing to its amplitude Over the femoral arteries, a snapping sound synchronous with cardiac systole, referred to as "pistol-shot" sound, and at times Duroziez' diastolic murmur may be elicited by putting gentle pressure over the femoral arteries with the diaphragm of the stethoscope The diagnosis of aortic regurgitation depends primarily on the presence of a classic diastolic murmur which is to be heard over the aortic valve and which extends downward along the left border of the sternum to the cardiac apex. Despite the absence of aortic stenosis there is frequently also a systolic murmur at the aortic area in pure aortic regurgitation as the result of the increased stroke volume output into the aorta with ventricular systole A presystolic apical diastolic murmur heard occasionally in isolated

sis and calcification may be important etiologic factors In addition to rheumatic etiologic factors for aortic regurgitation, there are subacute bacterial endocarditis, cardiovascular syphilis, dissecting aneurysm of the ascending aorta and aortic root, rheumatoid spondylitis and, rarely, physical or surgical trauma causing destruction of the aortic leaflets or dilatation of the aortic valve ring, which have produced aortic regurgitation

Aortic Stenosis

Clinical Syndrome

Usually, the typical patient with aortic stenosis has been aware that he has had a cardiac murmur for many years but has been unaware of subjective symptoms. With the passage of years the obstruction to the left ventricular ejection of blood becomes sufficient to result in symptoms of left ventricular failure or produces symptoms related to reduced systemic blood flow In this latter category is the occurrence of angina pectoris and the appearance of dizziness and syncope with physical exercise Despite this evidence of coronary insufficiency, acute myocardial infarction is uncommon Syncope and convulsive disturbance occur in approximately 10 per cent of the patients having aortic stenosis Unless the patient with aortic stenosis has his life ended abruptly with sudden death, symptoms of left ventricular failure, including effort dyspnea, orthopnea, pulmonary congestion and, finally, right heart failure, develop Control of chronic congestive heart failure due to aortic stenosis is difficult and discouraging as a rule, and death from congestive heart failure was found to occur on an average of 2.2 years after definite symptoms of myocardial failure had developed [1]

The characteristic peripheral pulse in aortic stenosis is of the plateau type and the peripheral pulse pressure is narrow On auscultatory examination, a loud, harsh murmur during systole is heard most loudly over the aortic valve and at the left parasternal line. The murmur radiates widely along the carotid arteries and also is heard well at the cardiac apex in many patients. A palpable systolic thrill felt in the aortic area characteristically accompanies the murmur. Its incidence appears to be directly proportional to the care which is given in searching for its presence. In most patients, the aortic second sound is absent or greatly diminished in intensity. Frequently, a short soft high-pitched diastolic murmur of aortic regurgitation will follow the aortic second sound. The presence of congestive heart failure or pulmonary emphysema will moderate and reduce the intensity of the typical murmur and thrill

Pathologic Physiology

Stenosis of the aortic valve orifice is productive of a definite chain of disturbances in hemodynamics Through experimental studies a rational interpretation of the clinical signs and symptoms of aortic stenosis can be developed [11] Narrowing of the aortic orifice up to 15 to 30 per cent is sufficient to cause the characteristic murmur, but experimentally the original diameter of the valve orifice must be reduced 60 to 70 per cent before cardiac output is reduced

Gorlin and associates[19] deduced that in pure aortic stenosis a valve area of 0 5 cm.^{2} is the critical level and that constriction to a smaller area is productive of disturbed physiology. At an orifice size smaller than the critical level, left ventricular hypertension must develop to produce pressure gradient across the aortic valve in order that cardiac output will be maintained This pressure gradient may reach 100 to 150 mg Hg at the expense of an appreciable increase in left ventricular work On exercise, the narrowed orifice and the already maximal effort on the part of the left ventricle cannot change, with the result that there is no rise or an actual fall in cardiac output and a rise in left ventricular diastolic pressure which is transmitted backward causing elevation of left atrial and pulmonary capillary pressures At this point, dyspnea or more dramatic symptoms of pulmonary congestion develop A chronic state of high pressure values in the left atrium and pulmonary capillaries eventually leads to added right heart failure As a consequence of the obstruction to left ventricular outflow, the arterial pulse waves show characteristic differences from the normal. The central and peripheral pulses assume similarity in form and

amplitude, the build-up time is prolonged, and there is an abnormal anacrotic pause.[12] Symptomatic coronary insufficiency, although it may be due to coronary atherosclerosis, also occurs as a consequence of obstruction of the aortic valve alone. Effort syncope in patients with aortic stenosis apparently results from cerebral ischemia.

Roentgenologic and Electrocardiographic Features

X-ray and fluoroscopic examinations of the hearts of patients having aortic stenosis supply both nonspecific and diagnostic evidence related to the valvular lesion. Nonspecific evidence is to be found in the presence of roentgenologic signs of left ventricular hypertrophy and enlargement. This may vary from slight to massive cardiomegaly in which the cardiac silhouette has the characteristic shape of a boot.

Definitive evidence for aortic valvular deformity usually of the stenotic type comes from the demonstration of calcification in the valve area (FIG. 11). Calcified aortic valve leaflets are detected as dancing x-ray opacities at the aortic root by the fluoroscopist.

The predominant electrocardiographic pattern is that of left ventricular hypertrophy. Electrocardiographic findings consistent with left ventricular hypertrophy were present in 68 per cent of a clinical series of patients who were operated on and these findings, together with left bundle branch block, occurred in 63.8 per cent of patients studied pathologically.[1] Atrial fibrillation occurs in only about 10 per cent of patients having pure aortic stenosis.[27] Despite the frequent occurrence of angina pectoris with aortic stenosis, myocardial infarction with characteristic electrocardiographic findings is a distinct rarity unless there is severe coronary occlusive disease. Conduction disturbances including bundle-branch block and complete A-V dissociation occur not uncommonly in aortic stenosis.

AORTIC REGURGITATION

Clinical Syndrome

Incompetency of the aortic valve leaflets which permits regurgitation of previously expelled blood from the aorta into the left ventricle during diastole may occur as an isolated cardiac abnormality or its effects may be tempered by simultaneous aortic stenosis. When the aortic leak is minimal, it may remain merely an auscultatory finding and may not produce either symptoms or hemodynamic abnormality. A significant leak, whether secondary to inflammation or trauma, is productive of symptoms secondary to left ventricular failure. Awareness of cardiac overactivity and fatigability are frequently symptoms prior to the onset of effort dyspnea. Angina pectoris and symptoms of cerebral ischemia occur less commonly than with pure aortic stenosis but still with appreciable frequency.

Examination of the patient with minimal aortic regurgitation may not reveal cardiovascular abnormality other than a short soft early decrescendo diastolic murmur, which is heard only at the left parasternal line with the patient's co-operation in leaning forward in a sitting position at full expiration. The significance of such a lesion is primarily its availability as a focus for the implantation of bacterial endocarditis.

In clinically significant aortic regurgitation, inspection will show the presence of prominent systolic pulsations involving the carotid arteries. Capillary pulsations can be demonstrated. Measurement of blood pressure reveals an abnormally high pulse pressure, with increased systolic pressure and decreased diastolic pressure contributing to its amplitude. Over the femoral arteries, a snapping sound synchronous with cardiac systole, referred to as "pistol-shot" sound, and at times Duroziez' diastolic murmur may be elicited by putting gentle pressure over the femoral arteries with the diaphragm of the stethoscope. The diagnosis of aortic regurgitation depends primarily on the presence of a classic diastolic murmur which is to be heard over the aortic valve and which extends downward along the left border of the sternum to the cardiac apex. Despite the absence of aortic stenosis there is frequently also a systolic murmur at the aortic area in pure aortic regurgitation as the result of the increased stroke volume output into the aorta with ventricular systole. A presystolic apical diastolic murmur heard occasionally in isolated



FIG 11 —Characteristic roentgenograms from a patient with calcific aortic stenosis (a) posteroanterior projection illustrating cardiac enlargement of left ventricular type, (b) RAO position showing convexity in region of pulmonary trunk and heavy deposit of calcium in aortic valve; (c) LAO projection illustrating posterior displacement of left ventricle and position of calcified valve and (d) lateral view to show calcification

aortic regurgitation is called the "Austin Flint murmur."

Pathologic Physiology

Characteristically, in dominant aortic regurgitation there is a heightened aortic systolic pressure due to the ejection from the left ventricle of a larger stroke volume; the larger stroke volume is a result of the added left ventricular volume caused by blood regurgitating into the left ventricle during diastole. Cardiac output is retained at near normal levels at the expense of increased left ventricular work by increasing the stroke volume by an amount equal to the regurgitated blood. The regurgitated blood through the incompetent aortic valve during diastole causes a rise in left ventricular diastolic pressure necessitating also a rise in left atrial pressure to ensure an adequate left atrioventricular pressure gradient.[4] This produces a measurable increase in pulmonary capillary pressure as well. When the left ventricle is unable to maintain adequate output without significant residual left ventricular diastolic pressure, the signs and symptoms of pulmonary congestion supervene and result in right heart catheterization pressure and flow values similar to those of aortic stenosis and mitral valvular disease. Peripheral arterial pulse waves reflect the aortic leak with high-systolic and pulse pressures and low-diastolic pressures which characterize the collapsing pulse of aortic regurgitation

Roentgenologic and Electrocardiographic Features

This hemodynamic valvular deformity does not produce characteristic abnormality on the routine roentgenogram of the thorax. When the lesion is marked and the heart is overworking, the previously described roentgenogram of left ventricular hypertrophy and dilatation is visualized The fluoroscopist is frequently able to predict the presence of aortic regurgitation by observing prominent pulsations of the aortic root and ascending aorta synchronous with each cardiac cycle.

Similarly, the electrocardiogram in aortic regurgitation reflects varying degrees of left ventricular hypertrophy and strain

Hemodynamic Data in Acquired Deformity of the Aortic Valve

Accurate physiologic methods for determining the severity of aortic stenosis and for determining the predominant defect when combined aortic stenosis and regurgitation are present are highly desirable now that surgical means for improving or correcting the defects are available.

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vular disease. The measurements for pressure and flow will be normal unless left ventricular failure has occurred, when the findings will be indistinguishable from those in mitral stenosis (Table 1).

Evaluating the characteristics of central aortic and peripheral arterial pulse contours is one hemodynamic approach for interpreting aortic valve deformity.[8] Normally, the aortic pulse recorded via arterial catheterization has an anacrotic shoulder and the peak of the systolic wave is rounded or plateau-shaped (Fig. 12) Peripheral arterial pulses, *on the other hand*, have a more rapid build-up to the maximum; there is no anacrotic pause and the maximum is peaked There is systolic amplification as the wave moves from a central to a peripheral point, so that the peripheral systolic arterial pressure normally exceeds that of the aorta In the presence of severe aortic stenosis, the peripheral pulse contour tends to approach the aortic pulse in form There is diminution or disappearance of the peripheral systolic amplification, prolonged build-up time in all pulses and the appearance of an abnormal anacrotic pause in the peripheral arterial pulse Aortic regurgitation, by contrast, shows rapid build-up to a high-peaked systolic summit in the aortic pulse, marked amplification of the systolic pressure as the pulse wave moves peripherally and disappearance or diminution of the dicrotic incisura The characteristic pulse contours are illustrated in Figure 12. These pulse contours, however, are usually inadequate in determining which is the significant lesion when both stenosis and regurgitation coexist and give *no information* concerning the size of the orifice



Fig 11 —Characteristic roentgenograms from a patient with calcific aortic stenosis: (a) posteroanterior projection illustrating cardiac enlargement of left ventricular type, (b) RAO position showing convexity in region of pulmonary trunk and heavy deposit of calcium in aortic valve, (c) LAO projection illustrating posterior displacement of left ventricle and position of calcified valve and (d) lateral view to show calcification

severer degrees of regurgitation. Braunwald has described a similar technic in Chapter 9 in which the dye is detected by an ear oximeter.

Another method of appreciable value in determining the degree of aortic regurgitation is to inject dye into a catheter whose tip lies in the aorta above the aortic valve and sample from the left ventricle via a needle inserted into the left ventricle. The amount of dye that is detected immediately at this sampling site represents the dye-blood mixture that has regurgitated into the left ventricle, and the ratio of the area of this initial early deflection to that recorded at the left ventricle after injection of the same amount of dye into the pulmonary artery will give an index of the severity of the regurgitation.[29] This latter method is also useful in evaluating regurgitant lesions of both the aortic and mitral valves. When a needle is also inserted into the left atrium by the suprasternal technic of Radner,[29] it is possible to inject dye into the aorta, left ventricle or left atrium, and to sample from the left ventricle or left atrium or from both sites simultaneously (Fig. 14).

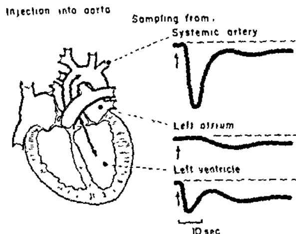


Fig. 14.—Schematic diagram of the paths taken by indicator injected into the aorta just distal to the aortic valve in the presence of aortic regurgitation. The dilution curves recorded from the systemic artery, left atrium and left ventricle are shown on the right. The instant of dye injection into the root of the aorta is indicated by vertical arrows. The indicator is immediately regurgitated through the aortic valve and thus is detected in the left ventricle prior to its arrival at the sampling site in the systemic artery. Since there is no mitral regurgitation, indicator appears at the left atrial sampling site only after traversing the systemic and pulmonary circulations.

Acquired Tricuspid Valvular Disease

Acquired chronic deformity of the tricuspid valve is uncommon when compared with the relative incidence of similar changes in the mitral and aortic valves. Although functional tricuspid regurgitation may be present commonly in severe heart failure of any etiology in which there is great dilatation of the right ventricle, its appearance as an organic lesion is almost always in conjunction with rheumatic tricuspid stenosis. It is important to recognize and differentiate tricuspid regurgitation from mitral regurgitation in the presence of mitral stenosis.

At necropsy, tricuspid stenosis has been found to be present in approximately 10 per cent of patients with rheumatic heart disease.[30] Although clinically apparent tricuspid stenosis is a serious cardiac lesion to the individual patient with rheumatic heart disease, from an over-all clinical standpoint it is relatively unimportant for two main reasons: (1) It occurs infrequently and (2) the clinical picture of the lesion is overshadowed by the effects of the more seriously diseased mitral and aortic valves. A diastolic pressure gradient across the tricuspid valve found at cardiac catheterization is diagnostic evidence of tricuspid stenosis.

Clinical Syndrome

A history of rheumatic fever was obtained in 78 per cent of Smith and Levine's group[30] of patients with tricuspid stenosis, and this is considerably higher than a similar history for any other valvular deformity. A history of long-standing chronic right heart failure in a young person who has severe or recurrent rheumatic fever should bring to mind the possibility of involvement of the tricuspid valve. While dyspnea with minor exertion is present, orthopnea and episodes of pulmonary congestion may be significantly missing from the patient's complaints. Fatigue, weakness and retention of peripheral fluid are prominent symptoms.

Physical examination will reveal the signs and findings of mitral or aortic valvular disease indicated earlier. Those findings related to the tricuspid deformity may be overlooked and attributed simply to severe congestive failure un-

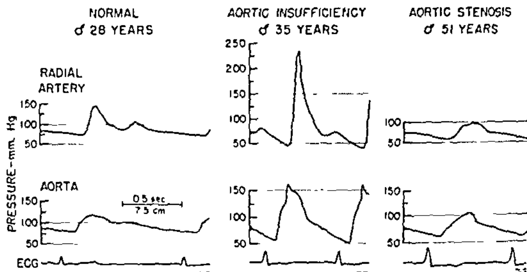


Fig 12.—Tracings of arterial pressure pulses of a normal subject, a patient with aortic regurgitation and a patient with aortic stenosis. The prolonged build-up time of the aortic pulse and lack of the normal increase in the peripheral systolic pressure in the patient with aortic stenosis should be contrasted to the opposite findings in the patient with aortic regurgitation. Central aortic pressures were recorded via a catheter threaded through an 18-gauge needle inserted into a femoral artery.

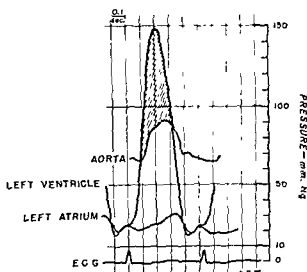


Fig 13.—Simultaneously recorded left atrial and aortic pressure pulses redrawn to scale and superimposed on left ventricular pulse. The patient is a 14 year old girl with aortic stenosis. The cross hatched area indicates the abnormal systolic pressure gradient across the aortic valve. The absence of a diastolic pressure gradient between the left atrium and the left ventricle excludes mitral stenosis.

A more direct approach is actual measurement of the systolic pressure gradient across the aortic valve which is accomplished by measuring simultaneously recorded pressures in the left ventricle and aorta. This may be accomplished by inserting a catheter into the aorta via the brachial or femoral artery, inserting a small-gauge needle directly into the left ventricle through the left anterior wall of the chest (the so-called Brock procedure) and recording the pressures.[8] This method is used occasionally in estimating the severity of stenosis immediately prior to surgical correction of this defect.

A more accurate method would be to utilize right heart catheterization combined with left heart and aortic catheterization so that the cardiac output as well as the pressure gradient might be obtained (Fig 13).

When aortic regurgitation coexists, the problem is more difficult. The left ventricular end diastolic pressure is usually elevated in patients with significant aortic regurgitation. However, this is not uniformly true and does not allow accurate assessment of the degree of regurgitation. The most promising methods seem to include utilization of indicator-dilution curves.

Warner and Toronto[32] have described a method for estimating the severity of aortic regurgitation by injecting the indicator into the aorta via a catheter advanced through a needle inserted into a femoral artery at varying distances from the aortic valve until no early appearing dye is seen at the sampling site from the right radial artery. The dye will be detected at the radial artery sampling site at further distances from the aortic valve with

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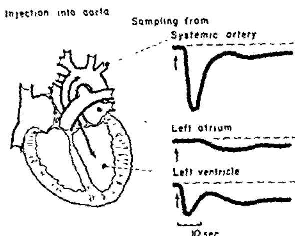


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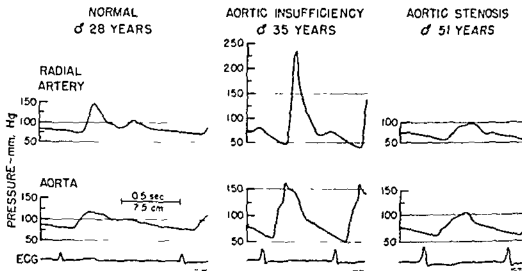


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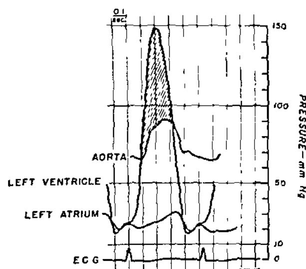


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Coronary Heart Disease

By JOHN J. SAMPSON, M.D

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THE functional and structural integrity of the myocardium, in part or whole, is dependent on the delivery of a blood supply adequate in quantity and quality for the work performed Quantity is dependent on volume of coronary flow as influenced by aortic pressure, the compressing effect of the surrounding contracting muscle and patency of the arterial lumen Other factors influencing coronary blood flow are discussed in Chapter 11

The constituents of the blood are equally important Although its oxygen content as determined by the hemoglobin concentration and oxygen saturation has been the most obvious factor, it is well recognized that the physicochemical changes involved in muscular contraction require the delivery and removal of many other substances than oxygen (Chapter 11). Among these with well recognized influences are carbohydrates, amino acids, lipids, lactic acid, pyruvic acid, ketone bodies, electrolytes, enzymes (especially coenzyme A), and thiamin, trace metals and water The major fuels for the processes of contraction are now recognized as carbohydrate, largely glucose, and unesterified fatty acids, especially in fasting or diabetic states High energy sources are the reactions converting adenosine triphosphate to adenosine diphosphate and lactic acid to glycogen.[7, 20, 47] The inherent nature of the myocardium may be altered as in diabetes, modifying its reaction to the materials delivered to it.[48]

The term "coronary insufficiency" is sufficiently broad* to cover the various degrees of inadequate blood supply to the capillaries of the myocardium The adequacy of blood flow is related to the immediate need as dictated by the work performed by the heart. The term will be used herein in the broad concept rather than such specific application of a single clinical pattern or degree of coronary insufficiency as in Master's definition of acute subendocardial focal myocardial necrosis caused by other factors than coronary artery occlusion

There should be a clear understanding that the term coronary insufficiency is applied to a functional state of inadequacy which leads to clinical syndromes, functional derangements or structural damage (Fig 1) Thus, the result may be a clinical syndrome of pain as in angina pectoris, transient electrocardiographic S-T segment depression and/or T wave inversion with acute hypoxia, or evidence of damage or destruction of the myocardial fibers in multiple minute areas or in single larger patches in acute myocardial infarction Such damage or destruction is generally diagnosed by clinical signs and symptoms of myocardial dysfunction, e. g, congestive heart failure, and by laboratory tests which indicate destruction of tissue Occasionally, the differentiation between transient myocardial dysfunction and reversible structural damage cannot be made promptly or prior to post-mortem examination Such is the situation in patients having spontaneous episodes of cardiac pain who do not exhibit electrocardiographic, erythrocyte sedimentation rate or serum enzyme changes typical of acute myocardial infarction Under these circumstances, the functional diagnosis of "acute coronary insufficiency" would seem acceptable. In the absence of other obvious causes, this functional state is probably due to coronary arteriosclerosis

The development of a critical level of coronary insufficiency inducing characteristic signs and/or symptoms of myocardial deficiency is dependent on both the myocardial work load and the coronary arterial circulation as modi-

* *Note:* Lack of space has necessitated condensation of references. References marked with an asterisk will be furnished by the author on written request.

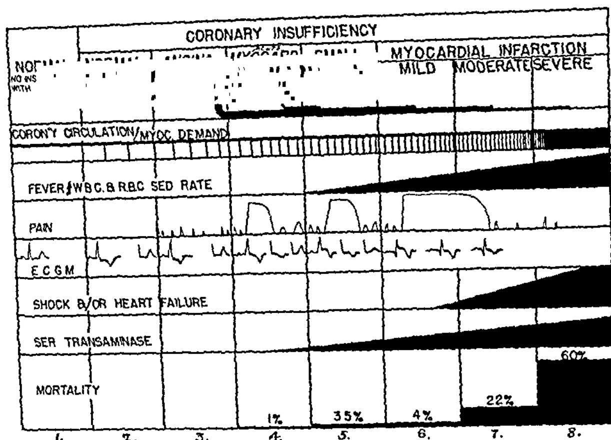


FIG 1 —Diagram of hypothetical increasing degrees of human coronary insufficiency—proportion of the myocardial requirement to the local or general available supply of oxygenated blood Columns 2, 3 and part of 4 represent evidence of functional inadequacy—largely reversible Column 3 Angina pectoris is a clinical term of variable functional and structural consequence Columns 4 to 8 represent structural damage of the myocardium of increasing magnitude, dependent on the duration and degree of coronary insufficiency

fied by occlusive disease of the coronary arteries with compensation by collateral circulation and other factors which influence coronary vascular caliber Occlusive disease is generally the primary cause, the other factors being precipitating mechanisms for the critical insufficiency Frequently, a precipitating cause cannot be found, but a precipitating mechanism, e g , severe hypotension, may initiate critical coronary insufficiency in a patient with no severe obstruction to coronary blood flow

The Causes of Coronary Insufficiency

If we accept the concept that coronary insufficiency is a disproportion between coronary blood supply and the work load of the myocardium, the causes may be divided into those that affect either the blood supply or the work load

Reduction of Flow Through Coronary Arteries

Occlusive arterial disease. This is generally arteriosclerosis, which presumes in most cases a basic endothelial or subendothelial degenerative process with intimal thickening, lipid deposits or atheroma in the subintimal and deeper portions of the wall and thrombosis on the abnormal internal surface The arteriosclerotic occlusion may be limited to a small segment or may be generalized in all three major vessels but rarely takes place within 1 to 2 cm. of the ostia. At least 50 per cent of a coronary channel may be obstructed for a centimeter without evidence of coronary insufficiency *

Other occlusive diseases of arteries are relatively infrequent and include emboli, polyarteritis, thromboangiitis obliterans, syphilis and aneurysms * Syphilitic aortitis or aneurysms of

the sinuses of Valsalva may distort and partially obstruct the coronary ostia, and cause aortic valvular incompetence resulting in coronary insufficiency and myocardial infarction. Dissecting aneurysms of the root of the aorta, often associated with Marfan's syndrome, may obstruct the ostia and produce myocardial infarction Rarely, a large neoplasm or aneurysm of the aorta may compress coronary arteries Trauma to the myocardium in chest compression injuries rarely may damage coronary arteries and precipitate thrombotic occlusions, but usually the myocardial injury is a result of the localized force * In the application of surgical procedures for the correction of constrictive pericarditis or defects of the valves, great vessels or septa, the coronary arteries may be damaged, ligated or constricted by distortion

The *distribution of the major coronary arteries* shows individual variations Schlesinger[42] presented post-mortem studies illustrating the three main patterns of dominant right coronary artery (48 per cent of all humans), balanced right and left coronary arteries (34 per cent) and dominant left coronary artery (18 per cent) The severity of myocardial infarctions seems to correlate with these patterns, probably due to differences in available collateral vessels, the most severe being the left dominant, intermediate is the right dominant, and least severe is the balanced pattern Infarction of the right ventricle is approximately one-fortieth as frequent as the left

Congenital anomalies of coronary arteries may lead to coronary insufficiency. These include a single right or left artery, communication between an artery and a vein, communication between an artery and a heart chamber, the left coronary artery arises from the pulmonary artery (*vide infra*) [13]

Compensation for partial or complete occlusion of coronary arteries generally occurs through recanalization of the occluded vessels or expansion of the collateral blood supply beyond the obstruction. There is conflict in the experimental evidence, because of different injection methods at necropsy, on the size and functional adequacy of the interarterial collateral vessels in the normal human, but they are obviously responsible for tissue survival after coronary occlusion.[35]* The gradient established in a collateral vessel between an open arterial channel with adequate pressure and a low-pressure channel in another artery distal to a partial or complete occlusion probably accounts *for the direction of flow* and gradual increase of the collateral channel's caliber.[10]* Intercoronary reflexes may contribute to dilating adjacent arteries after a coronary occlusion,[50] but the immediate effect is constriction of other coronary arteries *

Survival and myocardial competence both in experimental animals with coronary ligation and in man with coronary occlusive disease are increased materially if one or more factors are invoked which increase the development of collateral flow These factors include gradual narrowing of a coronary artery so that a *pressure gradient is established between* the open collateral and the distal portion of the constricted artery,[10] anemia and other causes of low arterial oxygen tension,[56] myocardial hypertrophy, partial constriction of the coronary sinus and aorta-coronary sinus shunt [6] Experimental studies also suggest that survival is increased by a moderate increase in physical activity during a partial arterial occlusion * Attempts to anastomose extracardiac arteries to coronary arteries have met with limited success Evidence has been obtained experimentally which demonstrates that increased retrograde flows are induced However, the therapeutic success thus far reported is insufficient to warrant widespread acceptance of these procedures This apparent discrepancy may be explained by the fact that the additional collateral coronary flow is neither placed in areas most needed, nor is it adequate for the need, since this extra flow *is only one-seventh of that developed after* gradual coronary occlusion.[20] Experimental, abrupt, complete coronary artery occlusion in dogs has been shown[20] to result immediately in less than half the necessary collateral flow to maintain muscle viability, but in 12 hours the flow may double and furnish the minimal survival requirement of oxygen. *In three to four* weeks, the collateral flow may approximate the normal flow of preocclusion

Another form of collateral blood flow is reported by Fulton* to consist of a heavy net-

work of small vessels in the subendocardial zones of hearts of patients with generalized occlusive coronary disease. This network apparently serves to distribute widely the reduced volume of blood and permits survival through an unusual economy of supply and utilization of blood by large areas of the myocardium

The compressing force of the contracting myocardium on the coronary arteries. In the normal heart systolic coronary flow is about one-half that of the diastolic flow because of the compression and constriction of vessels by the contracting myocardium, especially those vessels imbedded in the muscle In the perfused animal heart, asystole resulted in a 10 per cent increase in the left coronary artery inflow and a 50 per cent increase in coronary sinus outflow[29] Since the coronary flow is dependent on left ventricular output to maintain aortic pressure at the ostia, the inhibiting influence of systole on coronary flow is obviously to be disregarded in the normal heart[11] In the heart which is contracting with "high intraventricular pressure" but without increased aortic pressure (as in aortic stenosis), coronary insufficiency may be induced This is well illustrated by the disappearance of angina pectoris after surgical relief of either aortic or pulmonic valvular stenosis

Intrinsic factors influencing the caliber of the coronary arteries These factors may be divided into the passive influences on the coronary arterial tree proportionate to the head of pressure in the aorta and the coronary ostia, the relative reduction of the coronary arterial bed in relation to the total myocardial mass and the active modification of the coronary vascular bed by nervous, humoral or metabolic influences In most clinical states, these factors operate in varying degrees, as does systolic myocardial compression, to produce a summated effect of positive and negative influences on the coronary flow

In chronic hypertension without heart failure, coronary blood flow, cardiac output and oxygen consumption are normal, but coronary resistance (probably arteriolar) is high. This high resistance probably explains the abrupt development of coronary insufficiency when the systemic blood pressure is rapidly reduced to low levels in shock or by the use of hypotensive agents. Effective coronary blood flow in such a chronic state probably requires a higher than normal systemic pressure or a gradual adaptation to lower levels. Fatal acute myocardial infarction has been observed in a patient who, at autopsy, exhibited no severe coronary occlusive disease, but whose blood pressure fell from *180/110 to 100/70 mm. Hg after treatment* with autonomic blocking agents. Similar acute circulatory insufficiency has been observed in the brain and the kidney with use of such hypotensive agents

Hypotension from other causes, especially if abrupt, may induce coronary insufficiency and even myocardial infarction This may occur in such conditions as traumatic shock, hemorrhage, septicemia, diabetic acidosis, heat exhaustion, cerebral vascular accidents, large pulmonary embolism, drug idiosyncrasy, overdosage of vasodilator drugs, tachycardia or bradycardia of extreme degrees and certain vasovagal episodes.

In myocardial hypertrophy, the number, distribution and size of the coronary vessels have been thought by some investigators to be inadequate for the demand for blood, especially since the capillary supply does not seem to keep pace with the increase in muscle fiber length and diameter. Rodriguez and Robbins* have measured the volume of the coronary vascular bed by post-mortem injection and believe that it is increased in hypertrophied hearts but not proportionate to the hypertrophy.

An unusual example of local coronary arterial hypotension is presented in the congenital origin of the left coronary artery from the pulmonary artery. The flow in such an artery is into the low-pressure channel of the pulmonary artery and is derived from a large anastomosis from the right coronary artery

Stenotic aortic or pulmonic valve lesions prolong systole with a relative shortening of diastole. Similarly, tachycardia shortens diastole more than systole. Aortic insufficiency and other arterial "run off" lesions, e.g., patent ductus arteriosus, specifically diminish diastolic pressure with concomitant decreased coronary arterial inflow. Such patients are subject to

dilatation of the coronary vessels and enhance the coronary blood flow. When the maximum compensatory dilatation of the coronary arteries has been reached, the contractile efficiency of the myocardium decreases and higher ventricular filling pressure is necessary for a unit of stroke work In uncomplicated anemia, this state is not induced until the hematocrit falls to less than 30 per cent. Less severe anemia may induce coronary insufficiency in otherwise asymptomatic coronary arteriosclerosis. Cardiomegaly, which accompanies severe anemia, probably results from the higher ventricular filling pressure and dilatation that follows the myocardial failure as shown experimentally by depressed ventricular function curves [12]

Low oxygen tension in the alveolar air, as commonly observed at high altitudes and less frequently with faulty pulmonary ventilation or inhalation of high concentrations of an inert gas, parallels the effects of anemia Coronary vasodilatation occurs with lowered vascular resistance and a compensatory increase in coronary blood flow when the oxygen content of the arterial blood is below 5 5 volumes per cent *

The reverse phenomenon can be observed as a cause of coronary insufficiency The coronary flow slows with a high hematocrit and increased viscosity[20] beyond the level for which it would be compensated by the high extraction coefficients of oxygen from the blood or the vasodilatating adaptive mechanisms Thus, patients with severe polycythemia and hematocrits of 70± will exhibit anginal pain on effort and be free of such pain when the hematocrit is reduced to 50 There is invariably some "subclinical" coronary occlusive disease in such patients An additional hazard of polycythemia is the increased tendency for arterial intimal thrombus formation as a result of the slow flow and sludging phenomenon

As suggested above, carbohydrate and more specifically glucose is necessary in the maintenance of normal myocardial function Hypoglycemic states may precipitate coronary insufficiency by the accompanying hypotension but are suspected of contributing to myocardial damage by the inadequate supply of glucose Myocardial extraction and utilization of glucose varies within broad ranges with the arterial concentration of glucose In the diabetic, glucose utilization by the myocardium is relatively low for the height of the glucose concentration in the blood. Insulin increases myocardial glucose uptake relative to the lower levels of blood glucose incurred with treatment, however, this insulin effect will probably not compensate for severe hypoglycemia [48] Thus, theoretically and empirically, overdosage of insulin may be considered as damaging to the myocardium in patients with coronary disease as would glucose starvation In patients with acute myocardial infarction, parenteral glucose administration is a rational procedure when nourishment cannot be taken orally

The Work of the Heart

The definition of coronary insufficiency as an inadequate blood supply to the myocardium proportionate to the work of the heart implies that either factor may be responsible for this state However, it exists almost without exception in instances where the blood supply is defective as previously mentioned, since the compensatory dilatation of the coronary vessels to work demands is highly effective. It is conceivable that the coronary circulatory limits of a normal heart may be exceeded transiently by tremendous work demands Such evidence has been presented by Beckner and Winsor in the report* of one of 165 marathon runners exhibiting flattened electrocardiographic T waves and depressed S-T segments after a race, and of the double challenge of heavy work and 10 per cent oxygen inhalation reported by Yu and associates [54] Thus far, the factors responsible for the defective blood supply have been discussed, but these have relative degrees of severity and if mild may not become clinically apparent until augmented by excessive cardiac work

The stresses may be transient as with physical exertion or psychic tension, which probably initiate their cardiac responses through neurogenic and humoral mechanisms The result is increased stroke volume output, especially in the erect position, heart rate and systemic venous blood return with dilatation of the great veins and atria Persistent increased cardiac

work accompanies the increased metabolic demands and peripheral blood flow in thyrotoxicosis and fever, the increased resistance to expulsion of blood from a ventricle in systemic or pulmonary arterial hypertension and aortic or pulmonic valvular or infundibular stenosis, and valvular incompetencies or shunting lesions from high to low pressure areas in septal defects, large vessel shunts or peripheral A-V shunts.

In any of these clinical states, the commonest symptom of coronary insufficiency is anginal pain induced by the added work accompanying excitement, cold or physical effort. Ventricular enlargement and congestive heart failure are also signs of coronary insufficiency from these causes Occlusive coronary arterial disease, which may have been silent prior to the development of the dynamic stress, generally underlies the clinical state and adds the hazard of sudden death. Lessening of the stress may completely relieve the angina pectoris or congestive failure This is demonstrated by relief of the symptoms through successful therapy of underlying thyrotoxicosis or hypertension, section of a stenosed pulmonic or aortic valve, or closure of the shunts

The precipitation of myocardial infarction by emotional or physical stress seems to be well documented by many reports and by personal observations Lifting a concrete watering trough, carrying an injured companion up a hill, persistent vomiting, motion sickness and testifying in court, have all played etiologic roles in some cases of myocardial infarction. The mechanism of such infarctions has been attributed to subintimal coronary arterial hemorrhage, but in many instances no coronary arterial occlusion is demonstrable at autopsy, and the cardiac work/coronary blood supply imbalance concept has been invoked.

The medicolegal implications of these instances of myocardial infarction involve employment responsibility and compensation and therefore have been the source of much controversy Master* and others favor the explanation of such attacks as a coincidence in the natural course of the occlusive coronary disease since infarction often occurs at rest. Yater and associates,[53] and others* have reported a high percentage of the association of such stress to myocardial infarctions without coronary occlusion A greater proportion occurs during or immediately following periods of strenuous effort than during rest or quiet activity.

Manifestations of Chronic Coronary Insufficiency —Angina Pectoris

As a result of transient, fixed or progressive factors initiating coronary insufficiency, developing individually or collectively, the following clinical patterns may become evident:

The Cardiac Pain of Angina Pectoris

Cardiac pain in angina pectoris probably arises within the zone of the heart muscle and is most likely caused by local hypoxia from one or more causes of coronary insufficiency. It is the commonest evidence of coronary circulatory insufficiency. The cardiac pain of coronary insufficiency is somewhat analogous to the pain in an ischemic extremity such as that produced by a tourniquet or the pain of intermittent claudication precipitated by exercise. Lewis* termed the agents producing such pain as P substances. The sources of the pain stimulus have not been determined but probably are high local concentrations of certain incompletely oxidized metabolites. Lactic, pyruvic and phosphoric acids and potassium, histamine, acetylcholine, adenosine and phosphocreatinine have been suggested as likely suspects. The sites of the pain stimulus are also unknown, but the nerve end organs in the coronary artery walls (especially the adventitia), pericoronary nerve plexuses and possibly between the muscle fibers have been suggested.[51]

The pathways for the stimuli are discussed in Chapter 26 Cardiac pain, similar to other pain of visceral origin, seems to spread across several sensory dermatomes including the cranial as well as spinal nerve distributions In contrast, pain of thoracic or other sensory root origin, as in musculoskeletal disturbances, is more likely to be restricted to certain dermatomes with broader spread within their zones of root distribution.

Classical anginal pain is either constricting, compressing, expanding, aching, boring or

burning It may be a pressing discomfort or a numbness and heaviness—short of true pain. A strangling sensation, the "angina" of Heberden, with a feeling of impending death may accompany severe attacks It may be described by the patient as shortness of breath, but searching questions will develop the quality of discomfort as not true dyspnea or "panting" It is rarely, if ever, sticking, stabbing, sharp, darting or throbbing, and it is not augmented by breathing Its location is most frequently deeply substernal over several adjacent nerve root segments between the manubrium and the xiphoid process. Other areas of origin with a decreasing order of frequency are the transverse precordium, lower left anterior or lateral chest wall, upper midposterior thorax, right anterior chest wall, either or both forearms or upper arms, the lower or upper jaws and the high epigastrium I have never observed cardiac pain limited to areas lower in the abdomen Rarely the pain may migrate from a primary area to one or more of the other areas mentioned above

The pain commonly radiates either across the chest, toward either shoulder, down either or both arms to the fourth and fifth fingers, to the back, the neck, the ears, the cheeks, the palate and the tip of the nose It is unusual to have pain radiate down the right arm alone Often, numbness in the arms, elbows, wrists or fourth and fifth fingers will accompany anterior chest pain.

Anginal pain is initiated characteristically by physical effort or emotional stress and will persist generally for one to five minutes after the precipitating factor is terminated or a nitrite (usually nitroglycerine) is taken S A Levine terminates anginal pain by slowing the heart rate through carotid sinus massage * The degree of stress required to produce pain is often remarkably constant under similar environmental or bodily conditions Frequently, certain external or bodily factors consistently precipitate attacks although their mechanisms are unknown. The time of day is important. Anginal pain has been observed in patients in the early morning following one-half block of level walking, whereas later in the day the same patients can climb hills without discomfort. Minor effort late in the day, especially if the patient is fatigued, may cause pain although much greater effort earlier in the day was painless. After meals, minor effort may induce pain Exposure to cold on leaving a warm environment frequently incites pain In some patients, anginal pain is initiated only by walking against a cold wind Occasionally, a phenomenon of "second wind" has been observed wherein a patient may suffer moderate anginal pain after walking from one to two hundred yards; but with continued walking the pain gradually fades away. Katz* attributes this phenomenon to a myocardial metabolic adaptation with increased muscular and circulatory efficiency and lowered oxygen consumption following a period of increased heart rate and cardiac work.

The Clinical Course of Angina Pectoris

The typical patient with uncomplicated angina pectoris has occlusive coronary arterial disease and, in approximately 70 per cent of cases,[10] has at least one completely occluded coronary arterial branch. The onset of the anginal attacks may precede or succeed definite myocardial infarction, or may appear independently with pain of either fixed or gradually increasing severity.

Although the over-all prognosis of angina pectoris indicates a 15 per cent mortality the first year and 9 per cent yearly thereafter,[11] the individual pattern is variable. An entirely stable benign course of many years' duration suggests that the occlusive arterial disease is restricted in extent and nonprogressive, but without functional restitution by recanalization of occluded vessels or adequate collateral arterial development In other patients, there may be a gradual recession of symptoms and a complete clinical recovery Patients may have a limited period of spontaneous anginal attacks for one to eight months after a myocardial infarction with recovery due to adequate restoration of the vascular supply to the myocardium by collateral vessels and/or recanalization of occluded vessels. In many patients, the symptoms may increase either slowly or, more frequently, abruptly and intermittently Such progression suggests repeated acute occlusive

episodes, with or without demonstrable myocardial infarction. As the disease advances, the attacks of pain become more severe and more frequent and are precipitated by less and less stress until anginal pain at rest occurs spontaneously, particularly nocturnal angina (angina decubitus). Progressive destruction of myocardium almost inevitably leads to congestive failure, cardiomegaly and death.

Variants of Angina Pectoris

Patients with coronary heart disease and no other complicating cardiac or metabolic problem may have spontaneous episodes of anginal pain persisting for one-quarter to one-half hour and which may be resistant to nitroglycerine. These patients are frequently emotionally unstable The attacks may occur only at certain times of the day, even at night in bed, and appear to be unrelated to any apparent environmental influences Unusual fluctuations in daily frequency are observed At times, moderate physical effort will be tolerated without discomfort during a period when 5 to 20 spontaneous attacks occur daily. Such patients are a constant cause of concern to the physician as possible candidates for an acute myocardial infarction Peel* reports that between 10 and 30 per cent of acute myocardial infarctions are preceded by spontaneous anginal pains The causal mechanisms of these attacks are unknown but reflex coronary artery spasm, increased sensitivity to pain stimuli, local myocardial metabolic deviations and hormonal influences have been suggested

A variant of the classical Heberden type of angina pectoris is encountered in the somewhat younger, vigorous or athletic individual who can produce pain by an emotional excess (anger or excitement), but not by heavy physical work Such attacks again suggest a reflex coronary constriction

Another variant is presented by patients with constant high cardiac work loads, such as are seen in aortic stenosis, pulmonic stenosis, systemic or pulmonary hypertension and aortic insufficiency In such instances, the pain lasts 10 to 30 minutes, frequently occurs at rest and is not relieved by nitroglycerine. Here, the work load which induces the coronary insufficiency may not be affected materially by the peripheral or cardiac actions of nitrites Aortic insufficiency, other arterial "run off" lesions with low-diastolic pressures, tachycardias and the hypotensive states, are associated with reduced pressure in the important diastolic filling phase of the coronary arteries. This pressure may be further lowered by nitrites causing a "paradoxical" aggravation of the coronary insufficiency.

A variant described by Prinzmetal and associates* is characterized by spontaneous onset of pain not relieved by physical relaxation but relieved by nitrites and accompanied by an elevated S-T segment of the electrocardiogram in contrast to the depressed S-T segment observed during the "common type" of anginal pain. Angina may not reoccur after an attack of myocardial infarction.

Other Disorders Which May be Confused with Angina Pectoris

The diagnosis of angina pectoris as an exhibition of coronary insufficiency may be made readily by the display of characteristic pain under expected circumstances and relief in one to five minutes by rest or nitrites However, as suggested by the several variants mentioned, there are frequent cases in which the most meticulous inquiry into the history fails to differentiate this state from several others that may mimic it. The most troublesome and not uncommon situations are the coexistence of coronary disease and other causes of chest discomfort Some of the conditions most commonly confused with angina pectoris may be given:

Neuromuscular pains of the neck, thoracic wall and arms. The most frequent causes of these regional pains are physical fatigue, slouched posture and, occasionally, spinal arthritis The discomfort induced is a dull aching in these regions generally following nerve root distributions and often accompanied by left precordial darting pains Coughing, sneezing and motions of the upper trunk or arms may accentuate the discomfort. Tenderness may be elicited by heavy pressure over the ribs, intercostal spaces, and neck and arm muscles, often coinciding in spinal nerve root distribution

with tenderness of the same dorsal spinous processes of the cervical and upper thoracic vertebrae. Structural encroachment on a spinal nerve root, as in herniated vertebral disc or neoplasm, may produce a similar pattern. True myositis, fibrositis or periostitis has been described as in Tsietze's syndrome of the upper anterior costochondral junction area, and in strain of the pectoralis minor muscle.

Diaphragmatic hiatus hernia and esophageal diverticulum can cause a visceral type of pain identical with that of angina pectoris in its *character and radiation It may even be initiated* by physical exertion, especially bending and lifting The discomfort is generally centered in the epigastrium and likely to occur with the patient reclining. True anginal pain may be precipitated by this epigastric discomfort, and the two types of pain may become completely fused Gall bladder disease and functional or organic disease of the stomach or upper abdominal viscera occasionally cause symptoms difficult to differentiate from cardiac pain *There is no substantiation for the concept that* gallbladder disease alone can cause cardiac pain. The relief by nitrites of the pain resulting from gallstone colic or hollow viscus spasm may, at times, result in the erroneous diagnosis of angina pectoris

The pain of active pericarditis often is precordial but persistent and frequently radiates to the shoulders In contrast to anginal pain, it is generally increased by motions of the trunk or by deep breathing. Occasionally, the differentiation is extremely difficult, especially since the electrocardiographic changes of acute pericarditis may resemble those of myocardial infarction. *Typically, however, in pericarditis the* S-T segments are elevated without reciprocal depression and T wave inversion is delayed for four to six days. *Pleural pain is not likely to be* confused with coronary pain.

Chronic inflammatory or neoplastic disease of the deep tissues of the chest and penetrating aneurysms of the aorta may cause pain resembling anginal paroxysms.

The Electrocardiogram in Angina Pectoris and Chronic Occlusive Coronary Arterial Disease

The wide variations which may occur in the electrocardiograms of patients with occlusive coronary artery disease would be expected from *the extremes which are encountered in the* degrees of anatomic and functional encroachment of blood flow and in the resultant structural damage. Recognizing that most patients with angina pectoris have had at least one occluded coronary arterial branch, it is expected that some localized myocardial damage may well have occurred and be transiently or permanently reflected in the electrocardiogram Such damage may be clinically "silent" but initiate serial T wave inversions, which may be transient or permanent *This sequence* has been observed with the onset of typical angina pectoris or of a "minor" myocardial infarct Such a minor infarct may be manifest by somewhat more prolonged pain but without fever, rapid sedimentation rate or elevated serum glutamic oxalacetic transaminase activity. In other cases, if prompt blood studies are made, *some of these latter findings* may be diagnostic

A large majority of cases of angina pectoris without preceding myocardial infarction exhibit normal *resting electrocardiograms.*[41] It is not unusual to have an asymptomatic patient exhibit a normal electrocardiogram immediately before or even shortly after the onset of pain of an acute myocardial infarct

The persistent abnormalities observed in patients with chronic occlusive coronary disease are largely the following

1 Flattened, diphasic or inverted T waves in the anterior or left lateral leads with horizontal or semihorizontal electrical axes; T_{VL} flattened or inverted is generally abnormal. When the axis is vertical, the T changes are also seen in the posterior leads—V_F, II, III, *but flattened* T_{VF} *is often not* evidence of myocardial damage when T_{VL} is upright and the anterior chest leads are normal.

2 S-T *depression, especially* presenting a flat segment.

3 Blunted T waves and prolonged Q-T periods.

4. Inverted U waves, especially in the "transition" zone of the chest leads.

5. Bundle-branch block and *all degrees* of atrioventricular block appear "spontaneously" more often than accompanying characteristic major attacks of myocardial *infarction.* Such defects suggest minute infarcts of the conduc-

tion system. Persistent sinus bradycardia with heart rates of 32 to 45 indicate damage to the sino-auricular node. Wolff-Parkinson-White syndrome (short A-V conduction period with slurred QRS—predominantly in the upstroke, as the "delta wave") is observed more often than in the normal heart.

6. Aberrant rhythms, especially atrial flutter and fibrillation, are frequent, as are ectopic ventricular and atrial ectopic beats (often multifocal), and paroxysmal tachycardias. Whereas all of these arrhythmias may appear in hearts without disease, their occurrence in a coronary disease suspect enhances the probability of that diagnosis. Ventricular tachycardia is a therapeutically troublesome, dangerous and not uncommon sequel of myocardial infarction even months or years after the acute episode.

7. The dilatation and hypertrophy of the heart, almost invariably of the left ventricle, which follow both myocardial infarction and *chronic coronary* insufficiency produce electrocardiograms characteristic of left ventricular hypertrophy or strain.

8. Ventricular aneurysm as a sequel to myocardial infarction is accompanied by delayed QRS conduction, inverted T waves and often, by persistently elevated S-T segments in the *anterior* chest leads, presumably due to a local granulomatous pericarditis.

9. Finally, the extensive myocardial infarcts, most notably those transmural, leave in their wake permanent broad Q waves, S-T depressions and T inversions in the zones reflecting the healed *area of necrosis*. Since electrocardiographic abnormalities, especially abnormal T waves,[26] *may be induced by* many functional derangements of the heart, their diagnostic significance in suspected coronary disease is largely related to their placement in the clinical context of the case.

Other Diagnostic Tests for Chronic Coronary Heart Disease

Although ballistocardiograms have even less diagnostic specificity than electrocardiograms, abnormal ballistocardiograms *are obtained* with increasing frequency in individuals over 50 years of age. Since the report of Starr and Wood[16] of the high incidence of myocardial infarction in the months following the incidental findings of these abnormal records in a small series of presumptively normal subjects, there is a recognition of implied coronary disease in such findings. Cigarette smoking often induces these abnormalities especially in patients with coronary disease.*

The frequent failure to reveal objective evidence of coronary disease by resting electrocardiograms has led to the origination of stress tests to develop diagnostic alterations of the records.

During an episode of anginal pain, whether spontaneous or induced, there is a transient depression of the S-T segment and often flattening or inversion of the T waves, or *rarely* right-bundle branch block.[17] These changes were long observed after casual exercise even without pain induction, but Master and coworkers[30] contributed to the usefulness of such stress effect by standardizing the "two step" test.

The most disturbing features of this and other stress tests used in diagnosis of doubtful cases of coronary insufficiency are (a) the possibility of precipitating a myocardial infarction or other manifestations of acute coronary insufficiency (the test is not used *on obviously diagnosed cases or seriously ill patients*) and (b) the criteria for dependency of diagnosis,[31] especially the "ischemic" S-T segment depression.

A second stress test used for inducing critical electrocardiographic abnormalities is the *anoxemia test* of Levy,[27] the inhalation of 10 per cent oxygen and 90 per cent nitrogen for as long as 20 minutes. This test permits continuous electrocardiographic monitoring and the hypoxia may be terminated instantly by the administration of 100 per cent oxygen. The "anoxemia test" also induces S-T depression but is somewhat less sensitive than the exercise tests.

Manifestation of Myocardial Infarction and Coronary Occlusion

Coronary artery occlusion is not synonymous with myocardial infarction.[10] If there is adequate collateral circulation, a blocked *artery* may not induce muscle *necrosis* although the chances of its occurrence are very high; con-

versely, reduction of coronary circulation, as in shock, may precipitate infarction without arterial occlusion Snow and co-workers[45] believe that prolonged pain indicates an occlusion and that the duration and extent of the resultant ischemia will determine the extent of myocardial necrosis This time element may account for the 5 to 14 day delay (or longer) between the attack of prolonged pain and the exhibition of electrocardiographic and other laboratory or clinical evidence of infarction

T waves may invert temporarily (hours) after episodes of acute coronary insufficiency produced by hypotension, paroxysmal tachycardia or physical effort Similar is the effect exhibited by experimental transient ligation (20 minutes or less) of a coronary artery [33]

With permanent arterial occlusion, local hemorrhage, leukocytosis and patchy degeneration of the myocardial fibers are observed, with changes in the amino acid pattern and hexosamines in the muscle and release of enzymes * Plasma norepinephrine rise correlates with that of the glutamic oxalacetic transaminase * The patchy destruction of myocardial fibers observed experimentally after occlusion of an artery suggests the variable susceptibility of distant areas to the cessation of blood supply of a central coronary branch

The characteristic clinical pattern of myocardial infarction is. (1) the spontaneous onset of severe angina-like pain, unrelieved by nitrites and persisting for longer than one hour, (2) sequential localized electrocardiographic changes, including S-T segment elevation, T wave inversion, broad (over 0 04 second duration) Q wave development and often focal abnormalities, such as conduction defects and P wave variants, (3) hypotension; (4) pericardial friction rub; (5) fever; (6) leukocytosis, (7) rapid erythrocyte sedimentation rate and (8) elevated serum enzyme activities, especially glutamic oxalacetic transaminase (SGO-T) or lactic dehydrogenase (SLDH) early in the course of the attack in characteristic time patterns[40] The serum contents of copper* and manganese* also rise

In general, the smaller the infarct, the less characteristic would be the duration and severity of the pain attack and the fewer positive findings of other diagnostic criteria, but the diagnosis of even transmural infarcts may be obscured by atypical or masked symptoms *

The structural damage to the myocardium resulting from coronary insufficiency can be graded clinically as follows·

1 Minute areas of destruction and fibrosis occurring *without episodes resembling* the above pattern of acute myocardial infarction.*

2. Prolonged spontaneous episodes of cardiac pain frequently precede by days or a few weeks a major infarction * The use of multiple electrocardiographic chest leads has revealed that many of these attacks are in fact minor infarctions

3. "Minor myocardial infarcts" are classified more or less arbitrarily, and often are given the diagnosis of "acute coronary insufficiency "[22] Such cases are characterized by atypical pain episodes, serial inversions of T waves and occasionally S-T segment elevation. Prinzmetal and Kennamer* describe decreased R voltage and depressed S-T segments in similar minor infarcts These electrocardiographic changes frequently are localized to the anteroseptal zone None of the other diagnostic criteria of myocardial infarction are consistently observed but modest elevations of the serum glutamic oxalacetic-transaminase (SGO-T) or serum lactic dehydrogenase (SLDH) occur in approximately 40 per cent of the cases [40]

4 Episodes of characteristic myocardial infarction may be arbitrarily divided into three categories of severity· mild (good risk), moderate and severe (poor risk) The classification is made on the individual patient in relation to complications, sequelae and prognosis Russek et al * divided cases into "good risk" without preceding cardiovascular disease or serious complications, presenting a 3 per cent immediate fatality rate, and "poor risk" cases with a 60 per cent fatality rate Severe congestive heart failure and shock-like states persisting over one hour indicate an immediate fatality rate of 60 to 90 per cent; ventricular tachycardia or complete A-V block result in death in over one-half the cases

Heart failure, primarily left ventricular, is exhibited in the first post-infarction week in

nearly half of the 425 acute infarction cases studied by Ball and co-workers.[1] Roentgenkymograms in human patients frequently reveal the poor contractile quality of the myocardium.* The area surrounding the infarct may expand rather than contract during systole with a wastage of the contractile force Most of these areas regain their contractile quality, but some persist with local dilatation recognized as a ventricular aneurysm and are characterized by persistent heart failure.

Complications of Myocardial Infarction

Shock. In approximately 12 per cent of hospital cases a shock-like state develops with marked hypotension, sustained longer than one hour. The mechanisms responsible for this state are not entirely clear but Agress and associates[2] suggest that the reduced cardiac output results in hypotension in those patients who fail to initiate an adequate rise in peripheral arterial resistance This confirms the clinical impression that both cardiac and peripheral vasomotor phenomena contribute to the shock. Therapy of shock seems more effective when the agents, e g., norepinephrine and metaraminal, have both vasopressor (arterial and venous) and inotropic myocardial properties. The use of an extracorporeal pump to maintain arterial pressure in shock has been reported, but the evaluation has not as yet been published

Ectopic cardiac rhythms constitute a common complication of myocardial infarction during the first few post-infarction months[3] and usually are observed in the following frequency ventricular extrasystoles, 23 per cent; ventricular tachycardia, 3 per cent, atrial extrasystoles, 8 per cent; atrial fibrillation, 12 per cent; atrial flutter, 3 per cent, and atrial tachycardia, less than 1 per cent Although the precise physiochemical changes within the myocardial cells responsible for precipitating ectopic rhythms are not known, the loss of intracellular potassium has been suggested as one cause of myocardial hyperirritability Harris[21] found experimentally that ventricular ectopic beats arose in the zone of myocardium surrounding the necrotic muscle but with a low-tissue oxygen tension This is in agreement with Beck's* contention that a partially hypoxic heart is rhythmically unstable.

Conduction system and nodal defects are probably the direct result of the infarction, with either destruction of the conducting tissue or compression from edema and inflammatory tissue adjacent to the infarct.

Other serious complications of myocardial infarctions are:

1 Rupture of the ventricular wall usually with prompt death by tamponade, and generally occurring between the third and seventh postinfarction day. Rarely does this event occur in a heart diffusely scarred by previous infarction.

2 Ventricular septal rupture usually results in an abrupt load increment on the right ventricle and right heart failure. Death may follow from one week to months, but if the communication is small long survival is possible.

3 Rupture of a papillary muscle (about 70 per cent posterior) is a rare condition which initiates a mitral valve insufficiency accompanied by a systolic murmur and left ventricular failure.*

4 Thrombo-embolic phenomena represent an important group of complications. Mural thrombi are present at autopsy in 50 to 62 per cent of untreated cases of myocardial infarction and 32 per cent of those having received anticoagulant drug therapy.[52] Thrombi in deep leg veins are mainly the source of pulmonary embolism and mural thrombi of systemic arterial embolism in myocardial infarction.

Other Manifestations of Chronic Coronary Insufficiency

1. Congestive heart failure generally is a sequel to multiple destructive episodes of coronary occlusion and myocardial infarction, but may follow prolonged ischemia without acute infarction

2 Disturbances of rhythm or cardiac conduction are frequent, apparently spontaneous events. Paroxysmal ventricular tachycardia and complete A-V block are especially serious complications

3. Sudden and unexpected death (cardiac standstill or ventricular fibrillation) is of par-

ticular importance since approximately 20 per cent of all coronary deaths take this form.

Therapy of Coronary Insufficiency

Prevention of Intimal Thrombosis

Prevention of intimal thrombosis with resulting progressive occlusion of coronary arteries is the chief basis for the long-term use of anticoagulant drugs with a possible secondary effect, vasodilation.

Heparin administered parenterally in anticoagulant doses (generally administered subcutaneously as heparin sodium) seemed to diminish the frequency of immediate postinfarction anginal pains * Its use in smaller doses has an inconstant effect in clearing the four to five hour postprandial lipemia and preventing the accompanying attacks of angina[25] No agreement has been reached on benefits of intermittent doses, but daily administration is believed to prevent recurrent myocardial infarction *

The coumarin and indanedione drugs This orally administered group of drugs suppresses prothrombin formation and certain other clotting factors in long-term therapy Included are Dicumarol (bishydroxycoumarin), warfarin (Coumadin) and phenylindanedione which have been used extensively Among others are Sintron (acenocoumarin), Cumopyran (cyclocumarol), Tromexan (ethyl biscoumacetate) and diphenadione. They vary in their therapeutic dosage requirements and to some degree in the speed of action and dissipation. Their toxic effects, other than tendency toward hemorrhage, are inconsequential except for intestinal irritability and alopecia (reversible) in coumarin therapy and a very rare occurrence of hepatitis, skin eruption or agranulocytosis in use of indanedione drugs.

Recently, there has been presented increasingly convincing evidence that long-term anticoagulant therapy prevents recurrent myocardial infarction and prolongs life. These include Nichol and associates,[32] Suzman and Goldberg* and Peel * The latter investigator selected, as favorable candidates for therapy, only those patients who had a rapid "heparin retarded coagulation time" These reports fail to present the meticulous double-blind control of the treated and untreated groups in arriving at their conclusions Such methods were employed by Bjerklund,* Owren* and a "Working Party to the British Medical Research Council.[34] The conclusions of the latter group were that the over-all incidence of recurrent myocardial infarction was approximately halved, but the major reduction in fatality rate was demonstrable only in the first three months after an infarction. There was a continued reduction in incidence of recurrent infarcts for at least two years to approximately one-fifth of that of the control group in males under the age of 55 years, and to one-half over that age. The effect of this therapy on either mortality or reinfarction could not be established statistically in women probably because of the small number included in this series

Plasmin (streptokinase-activated fibrinolysin) given by intravenous drip exhibited striking properties in resolving experimentally produced coronary thrombi[39] in dogs and apparently in human coronary thrombosis as indicated by improvement of objective clinical signs. Danger of hemorrhage required monitoring of all phases of the clotting mechanism, especially the fibrinogen production.

With incompetent management, anticoagulant therapy is highly dangerous Generally, but not invariably, prompt intravenous use of vitamin K will terminate serious bleeding in one to four hours. The use of anticoagulant therapy is governed by the skill of the attending physician and the precision of laboratory determinations, especially "prothrombin times" There is not uniform agreement on the ranges of "prothrombin activity" considered effective, dangerous or ineffective Appreciation of the influence and the measurement of other clotting factors should improve this uncertainty.*

The contraindications to an anticoagulant regimen include any potential hemorrhagic diathesis, ulceration, especially of the gastrointestinal or urinary tract, recent trauma to the brain or spinal cord and severe hepatic or renal disease An important contraindication is the patient who cannot, or will not, fully co-operate with the physician Hemorrhagic pericarditis

with fatal cardiac tamponade and rupture of the heart has apparently increased in frequency with use of anticoagulant therapy[4] in acute myocardial infarction.

Coronary Vasodilating Agents

Nitrites. The action of these drugs has been previously discussed, including the relation of the coronary vasodilator effect to the work of the heart and to the peripheral vascular influences, and reasons for failure of favorable patient response. There is no doubt that the rapid acting nitrites, amyl nitrite and nitroglycerine, are the best available means of controlling anginal attacks except for exclusion of precipitating factors. Longer acting orally administered nitrites, namely erythrol tetranitrate, pentaerythrol tetranitrate (Peritrate), which are more effectively absorbed sublingually, mannitol hexanitrate and triethanolamine trinitrate (Metamine), have been used to prevent induced or spontaneous attacks, as have preparations slowly releasing nitroglycerine internally or through the skin. Daily rationing of these drugs has not generally achieved their objectives, although attacks specifically occurring at certain times often will be prevented by timed prophylactic administration.

Alcohol. Long experience indicates that the intake of 1 to 2 ounces of a spiritous liquor (30 to 50 per cent alcohol content) will terminate an attack of angina pectoris even when nitroglycerine is seemingly ineffective. Russek and co-workers* believe the effect is psychic, but Lesher and associates,* showed experimentally on dogs that dilute alcohol infusions materially increased coronary blood flow.

Other drugs. Certain other drugs which experimentally cause coronary arterial dilatation have seemed, with daily oral rations, to diminish the frequency or severity of anginal attacks but with poor consistency. They include (1) the xanthines including theobromine, theophylline and aminophylline, (2) khellin; (3) papaverine and Paveril (dioxyline phosphate), which like khellin often causes nausea and anorexia, (4) quinidine and quinine; and (5) the coumadin drugs and heparin.

Drugs Possibly Modifying Source of Pain

Relief of muscular pain and angina pectoris by the amino-oxidase inhibitor iproniazid was reported in 1957 by Cesarman.* Its action was presumed due to the local suppression of pain factors in the muscle and to possible general vasodilation by increased concentrations of serotonin and of the coronary arteries by catechol amines. Cossio[14] found the effect of iproniazid and isoniazid was especially beneficial in skeletal pain induced by ischemia. Fatal hepatitis follows isoniazid therapy in rare instances so that several new drugs of this class but with less tendency toward toxicity have been introduced.* Their effective dosages and therapeutic values have not been finally assessed relative to their toxicity which included psychic irritability, hypotensive tendency and potential liver damage.

Procedures Diminishing Cardiac Work

Restriction of physical activity. The physical activity in patients with chronic coronary insufficiency should be restricted to the extent that the demand for blood by the myocardium will not exceed the supply. Even a transient imbalance of this demand supply ratio may result in irreversible myocardial damage. On the other hand, too severe restriction of activity may result in invalidism with resulting economic strains, emotional problems, loss of muscular efficiency, vasomotor competency, and possibly venous stagnation and thromboembolism. A midway course is generally chosen in which the occurrence of anginal pain serves as a general guide for limiting activity. In patients with repeated spontaneous anginal attacks, a period of 7 to 14 days at maximal rest in bed or on a couch may terminate these pains.

The degree of activity permitted in patients with acute myocardial infarction is becoming more liberal as the ill effects, as contrasted to the limited benefits, of prolonged bed rest are recognized. The completeness of the bed rest and its duration are largely dependent on the size of the infarct and its sequelae. If the patient is not in shock, the use of a bedside commode and the early transfer to an adjacent chair for several hourly periods during the day seems not only harmless but beneficial.[27] In patients

with minor infarctions, ambulation has been permitted, and apparently safely, by the first week after the onset of the attack, with return to light work by the fourth week.

Sodium restriction and diuretics. Some patients with angina pectoris have benefited from restriction of dietary sodium and the use of diuretics Most, but not all, of the patients who improve with this regimen have some degree of congestive heart failure It seems probable that diuretics and sodium restriction act by reducing the circulatory blood volume, thereby lessening the work load of the heart with resultant improvement in myocardial metabolism

Suppression of thyroid activity Although Blumgart, Levine and Berlin in 1933[9] reported favorable results with "total" thyroidectomy on euthyroid cardiac subjects, the procedure fell into disuse because of the difficulty of maintaining a balance between disabling myxedema and cardiac symptoms

Greater success in controlling angina pectoris has been achieved with newer agents such as radioactive iodine (I^{131})[9] and the antithyroid thiourea drugs such as propylthiouracil.[37] These thyroid suppressive agents generally do not cause the profound hypothyroidism induced by total thyroidectomy

The most obvious beneficial influence of either medical or surgical thyroidectomy is the reduction of the work of the heart as a sequel to (a) the reduced metabolic demands of the body and resultant reduction in blood flow, (b) specific reduction of myocardial metabolism, (c) reducing emotional overactivity and its influence on cardiac output and (d) diminished sensitivity to epinephrine.

Surgical Measures for Treatment of Coronary Disease

The surgical therapy for coronary insufficiency has included two general types interruption of the sensory and vasomotor nerve pathways of the heart and improvement of the coronary circulation.

Section of nerve pathways The partial interruption of autonomic nerve pathways of the heart has been accomplished by (1) paravertebral block by procaine or alcohol of the first to 4 or 5 thoracic sympathetic ganglia,[51] (2) section of the sensory roots of the same nerves and (3) by cervical-thoracic ganglionectomy.[51] Pain has been prevented in a significant number of cases, and there is some evidence that coronary blood flow may be increased, but prognosis of life expectancy is uninfluenced Because of the relative uncertainty of results and the surgical risk, these measures have been advised primarily for patients with intractable angina who fail to respond to other therapy.

Improvement of coronary circulation. The operations previously and currently employed for improving coronary circulation include (a) application of a graft of omentum, intestine, lung, pectoral or intercostal muscle, (b) anastomosis of an internal mammary artery with a coronary artery or an implant of such an artery end into the myocardium*, (c) arterialization of the coronary sinus, with coronary sinus constriction, by anastomosis with the aorta[20], (d) ligation of the internal mammary arteries theoretically increasing backward pressure in the mediastinal collateral arteries. This procedure although quite simple has not proved effective*, (e) the production of pericardial adhesions with vascular channels between the chest wall and the myocardium This procedure involves mechanical or phenol denuding of the pericardium and introduction of pericardial irritants* or polivinyl sponge*, and (f) removal of obstructing lesions from the coronary arteries,[4] a somewhat hopeful surgical approach but as yet too recent to be thoroughly evaluated as to benefits and risks.[29] None of the other procedures receive wide acceptance

Pathogenesis of Coronary Arteriosclerosis[16, 55]

Although arteriosclerosis may exhibit highly selective localization in the coronary and other arteries, there are great differences in the structural abnormalities of the arterial walls, which suggest that there may be variations in the basic origin of occlusive arterial disease. At least four pathologically different coronary occlusive patterns have been described:

1. Intimal spiral or longitudinal bands of muscle fibers, collagen, ground substance and elastic fibers may be increased in the epicardial arteries (as early as birth in males) and with greater thickness of the arterial walls *

2 Subintimal fibroblast proliferation and excessive deposition of mucoid ground substance have been found in male human fetuses and new born infants.* In females, this process appears later in infancy These changes may in the young adult advance to an occlusive state* and in later life may contain increasing amounts of lipids. Mural thrombi have been suggested as the source of this nonlipid material *

3 Deposition of cholesterol-containing lipids in the coronary and other arterial intima was observed many years ago by Aschoff* in infants. Recently similar depositions were seen in chick aortas perfused by lipid-enriched blood * Variation of tissue permeability including hyaluronidase content may well influence lipid deposit.* These lipids often disappeared or receded following the suckling period in animals In humans, the recession is less striking, and in adolescent males* there is a striking rise, which again recedes after the age of 20 years.

Synthesis of cholesterol and other lipids in the arterial wall has been demonstrated by Siperstein and associates* and others This mechanism for lipid deposit may be more dependent on the individual metabolic tissue variance than the lipid content of the blood.

4. The combined atherosclerotic and fibrotic lesion has been considered to represent primary injury to the internal elastica and to the media Such lesions have been ascribed to (a) the continued trauma of the pulsating volume and pressure of the contained blood, (b) unknown metabolic, inflammatory, hyperallergic or degenerative agents and (c) plaque formation with increased vessel ingrowth from the lumen and vaso-vasora

Rupture of minute vessels with hemorrhage into the plaques may occur early and extend the damage and scarring of the wall, or may balloon the intima into the lumen to cause an acute occlusive episode

Some of the factors which appear to bear on the development of occlusive coronary artery disease follow:

Hereditary Influences

Inheritance of possible metabolic qualities The incidence of coronary disease in siblings or children of coronary patients is twice as great as in those without such a family history.* Furthermore there is a definite individual and familial association of hyperuricemica and gout with coronary artery disease,* and 60 per cent of parents or siblings of young coronary patients have exhibited hypercholesterolemia.*

Genotype. The broad-chested, athletic mesomorph has a greater chance of developing coronary atherosclerosis than the other genotypes.

Sex. Overt coronary disease in premenopausal women without such complicating diseases as diabetes or hypertension, is one-nineteenth as common as in males, after the age of 60 years, this ratio was 1 to 2; and after the age of 70, 1 to 1.*

Race. The social, dietary and emotional elements that may modify the incidence of arterial disease in different races in different habitats have largely negated any estimates of a purely hereditary racial disposition or resistance to such disease

Psychological, emotional and hormonal interrelated factors which seem to govern the susceptibility to stress and, in turn, to hypercholesterolemia and coronary disease.

Blood lipids Certain associations have been established between the predictability, incidence and progress of overt coronary disease and the inherent level of certain blood lipids,* especially cholesterol and the beta lipoproteins * Likewise, there have been numerous competent studies indicating that blood lipid levels may be altered to approach the pattern of the "normal" man. The assumption that such modifications of the lipids necessarily will affect the incidence or course of coronary disease is not well supported by available evidence

The reduction of postprandial lipemia,* including a 24 hour delay in disposition of fed radioactive triolein,* the capacity of heparin to clear lipemia and the disposition of intravenously injected cholesterol are impaired in certain arteriosclerotic patients Williams and associates* observed, in anginal patients as contrasted to normal control subjects, that after meals the blood viscosity increased with cell clumping and a slowed circulation in the small conjunctival vessels of the human

Primary hyperlipemic states. Accelerated occlusive atherosclerosis accompanies marked

idiopathic hypercholesterolemia with or without xanthelasma, tuberous or tendinous types of xanthomatosis.* Even where the blood plasma cholesterol reaches 1.0 Gm 100 ml, the relation may not be causal since the serum cholesterol concentration as in diabetes does not seem to parallel the severity of the atherosclerosis Myxedema and nephrosis with high blood lipid have a suggestive but no certain causal relationship to precocious or excessive atherosclerosis

The ill effects of lipemia and hypercholesterolemia have been mentioned in part previously, but the tendency toward increased blood coagulability was recently analyzed by Nitzberg and co-workers * The Stypven time (Russel Viper Test) was the only clotting factor found to be accelerated, and this occurred in hyperlipemia but not in hypercholesterolemia

The Environmental Influences on the Blood Lipids and Atherosclerosis

Diet The current lay and medical interest and participation in dietary prophylaxis and therapy of arteriosclerosis stems from several facts: (a) The atherosclerotic plaque is known to contain cholesterol (b) Cholesterol feeding in certain animals causes elevated blood cholesterol levels and atherosclerosis, although infrequently in the coronary arteries without other challenging factors (c) Epidemiologic surveys have indicated that certain groups of people with a low incidence of coronary disease eat far less fat than of that ingested by American and most "Western peoples" with high standards of living.*

The general population is now aware of the serious toll of illness and death taken by coronary disease, especially in the productive age of the male adult, and it exerts pressure on the medical profession to alleviate this situation. Despite the many active research projects under way in the world, there is little that can be done to satisfy the public demand Diet, be it low calorie, low fat or low saturated fat, is therefore seized on as one of the main hopes of stemming the catastrophic coronary tide, although favorable results are not as yet well documented in man. Long-term anticoagulant drug therapy is the other current hope for bettering the prognosis of coronary disease That the occlusive process may be reversed in the adult human is possible, as strongly suggested by results on experimental animals *

Total calories and obesity Obesity generally implying excess caloric intake has carried a high mortality rate from vascular disease in actuarial data of insurance companies in autopsy studies of Wilkin and associates,* and in certain surveys, most notably the Framingham project (Dublin and Marks) * When, however, hypertension and diabetes are excluded, Keys and others* report no correlation between coronary disease, blood cholesterol and overweight except at extreme ranges (greater than 40 per cent).

High total fat diet There seemed to be a temporal parallel between coronary mortality and variations in diet especially the fat content, as noted during the war years 1940–1946, especially in Great Britain and Scandinavia. These correlations have been questioned on statistical grounds [55] There has been an apparent increase of occlusive coronary and other vascular thrombotic tendencies more than an increase of generalized arteriosclerosis in necropsy studies

Unsaturated-saturated dietary fat ratios. A relatively greater proportion of low-to-high-saturated fat diets* as first reported by Kinsell and colleagues has led to a wave of popular trial of such diets but with avoidance of weight gain. These are polyunsaturated fats and the "essential" fatty acids which are found in the vegetable or marine animal oils Two interesting actions of unsaturated fats which may have clinical implications have been reported: (1) Grieg and Runde* find that fibrinolysis is inhibited by saturated fats and accelerated by unsaturated fats (2) Rutstein and associates* found that aortic intimal cells in tissue culture preparations engulf cholesterol from the medium more rapidly when (saturated) stearic acid is added. Unsaturated linolenic acid inhibits this phagocytosis

Physical exercise There is some medical support of physical exercise to improve coronary circulation and to maintain caloric balance. Exercise can lower blood cholesterol content or prevent its rise in humans on high

fat-high calorie diets, and experimentally it increases collateral coronary circulation *

Stress and behavior pattern (personality). Stress may be severe externally or internally but it is exhibited chiefly as environmental impacts on an inherited behavior pattern characterized by an intense drive, competitive urge, conscientious efforts to meet deadlines and general alertness. The human male's increasing pace of competitive effort in modern life suggests an association with increasing frequency and prematurity of coronary artery disease. A definition of stress in terms of this effort contrasts (1) personalized stress, as executives incur in a competitive business, with more damaging effects than (2) group stress, e g , city bombings during a war The influence of stress on both blood lipids and on tendency toward coronary disease has been reported by Russek,* Friedman and Rosenman,* and others *

Other Influences on Blood Lipids and Coronary Arteriosclerosis

Schroeder* has reported an inverse correlation between coronary disease and the "hardness" of water in different areas of the United States

Tobacco No direct physiologic proof exists that coronary blood flow is decreased by tobacco although abnormal changes are produced by smoking in the "exercise electrocardiogram" and the ballistocardiogram * Anginal pains may be induced by smoking in "sensitive" coronary patients Heavy chronic smoking materially increases the incidence of and mortality from coronary disease according to Hammond and Horn,* and Breslow and Buechley.*

Alcohol There is no direct association of chronic excessive alcohol intake with coronary disease. Blood serum cholesterol and total lipid content will rise after intake of alcoholic drinks, but no relation to atherosclerosis is established by these transient changes or to more persistent high levels The latter is probably due to hepatic or pancreatic disease *

Estrogens Katz and Stamler* and others have reported that estrogen therapy may influence human as well as experimental animal atherosclerosis, and in 25 mg daily doses may reduce the serum β-lipoproteins in women Hormones are being sought that accomplish these ends without unpleasant feminizing influences on men.

Inhibitors of cholesterol synthesis Inhibitors of cholesterol synthesis have recently been suggested as important prophylactic or therapeutic agents in hypercholesterolemic atherosclerosis. Reports have been presented indicating significant inhibition of C^{14} acetate incorporation into cholesterol in rats and a fall of cholesterol content in the liver, the aortic wall, the bile and the serum In minimal effective oral doses in rats and monkeys, no toxic reactions were observed in a six month period of continuous use. The products tried by Steinberg* and Frederickson, Blohm and associates and others, were β-phenylbutyrate* and 1-[(4-diethylamino-ethoxy)phenyl]-1(p-talyl)-2-(p-chlorophenyl) ethanol, "MER-291 "*

Thyroid hormone isomers. Thyronine has been found to lower serum cholesterol without the undesirable elevation of the metabolic rate

Conclusions (Pathogenesis)

Occlusive arteriosclerosis encompasses at least two, and perhaps more, structurally different processes. In one such process, fibrous and hyaline-like material is deposited in the artery, and in the other there are depositions of cholesterol and lipids Either process may be primary, but the lipid deposits more often are secondary. Hemodynamic trauma and thrombosis are possibly related to the former and high content of blood lipids to the latter. Inherent deviations of the metabolic activities of the arterial wall are undoubtedly important in the genesis of either process. The coronary arteries may be more or less susceptible to the processes than the aorta or other arteries.

There are thus structural, dynamic and hereditary factors which may be considered primary and metabolic, or environmental factors, such as diet and stress which may be either primary or secondary Experimental and statistical studies reveal certain strong associations and lead to recommendations for prophylaxis or therapy. However, in the problem as applied to man, there is frequently so much individual variation in response to supposed

causative agents that clearly defined conclusions are not always possible Caution should thus be exercised before applying prophylactic or therapeutic measures, on a widespread basis, to insure that the procedures are harmless and that there is a reasonable likelihood of accomplishing the desired objectives Within the framework of this reasoning it would seem acceptable at present to use low-caloric, low-saturated fat diets and anticoagulant therapy in individuals known to have occlusive arterial disease and at least modification of stress-inducing patterns of life where possible on candidates for such disease

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Pathogenesis of Organic Changes in Chronic Hypertension and Hemodynamic Effects of Antihypertensive Agents

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THE characteristic hemodynamic abnormality in hypertension is the increase of total peripheral vascular resistance. All other possible factors such as cardiac output, total blood volume and blood viscosity are normal in uncomplicated essential hypertension, but when unduly elevated might produce a rise of blood pressure. Except in rare instances, as in patients with pheochromocytoma, the cause of the vascular constriction is unknown.

Despite the present ignorance concerning the etiology of chronic hypertension, there is considerable evidence to suggest that the pathogenesis of organic complications is connected directly to the elevation of arterial pressure. The characteristic pathologic lesion is hyperplasia of the intima of the arterioles. It was considered previously that this change, as a primary process, produced the increased peripheral resistance, resulting in hypertension, the impression having been gained from autopsy examination of patients dying in the advanced stages of the disease

It is known that proliferation and fibrosis of the arterial intima are not found early in the course of benign essential hypertension Biopsies of muscle and also of kidney as well as autopsies in young hypertensives dying of other causes fail to reveal structural changes in the intima of the arterioles Arteriolosclerosis, therefore, is a late development. In the early stages, the constriction is *functional* —a narrowing due to smooth muscle contraction. This functional constriction often can be seen in the optic fundi of patients with significant hypertension of relatively short duration. More interesting, the spasm may subside when the blood pressure is reduced. Byrom has shown this reversal to occur in the meningeal arterioles of hypertensive rats.[1] Relaxation of arteriolar spasm has been seen in the optic fundi in patients with short-lived hypertension such as acute nephritis or toxemia of pregnancy when the blood pressure was reduced with antihypertensive agents or following recovery from the acute hypertensive state. Reversal of fundic arteriolar spasm may also occur in young adults with chronic essential hypertension after their blood pressures have been controlled at normotensive levels with antihypertensive agents.

Since the sclerosis of arterioles follows the hypertension by some years, it seems possible that the condition is produced by the hypertension per se or by the associated arteriolar spasm. Evidence supporting this concept has been supplied by Wilson and Byrom.[1] They induced hypertension in the rat by constricting one renal artery with a partially occluding clamp. As a result, distal to the clamp there occurred not only reduction of blood flow but also of blood pressure. A severe hypertension, however, developed in the remainder of the animal, including the arterial branches of the opposite kidney. In the animals who died of severe hypertension, typical arteriolosclerotic and arteriolonecrotic lesions were found in the vessels of the opposite or high-pressure kidney, whereas in the low-pressure kidney distal to the clamp the arterioles appeared quite normal.

Some instances of hypertension associated with narrowing of a renal artery in man suggest that human arterioles react similarly. For example, in patients with hypertension secondary to partial thrombosis or other forms of narrowing of one renal artery, intimal proliferation of arterioles is found in the opposite kidney but seldom in the involved kidney. Bland

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causes atherosclerosis but rather to indicate that the hydraulic effect of an increased pressure head existing within the arterial tree hastens and intensifies the process of lipid deposition

Congestive Heart Failure

It has been recognized for many years that the left ventricle responds immediately to an increased peripheral resistance by dilation and somewhat later by hypertrophy The dilatation is purely a mechanical response conditioned by the contractile properties of cardiac muscle. If the peripheral resistance is elevated, the ventricle fails to empty as completely as it had previously As a result, the volume of residual blood increases in the ventricle producing further stretching of the myocardial fibers According to Starling's law, cardiac output is proportional to diastolic fiber length, the greater the stretch the greater the subsequent contraction As a result, the output is restored to normal despite the elevated aortic pressure.

It should be noted, however, that in order to maintain a normal output the contraction of the heart muscle is increased, this requires a greater expenditure of energy (increased work) As with any muscle subjected to prolonged work demands, the fibers hypertrophy and the ventricular wall thickens.

Eventually, if the hypertension becomes more severe, or if the blood supply to the myocardium becomes compromised by atherosclerosis of the coronary arteries, or if the myocardial musculature becomes diseased through other causes, a point is reached in which further diastolic stretching leads to less effective rather than more effective contraction It was demonstrated by Starling and later amplified by Sarnoff that there are limits to the compensatory powers of cardiac muscle. In every myocardium there is a critical point at which further stretching of the fibers leads to less effective contraction and the cardiac output falls Once this point is passed, additional increases in arterial pressure evoke progressively poorer contractions with a consequent rapid decline in output. If the heart is damaged from other causes such as coronary artery disease or myocardial fibrosis, this critical point occurs at lower aortic pressures than in an undamaged heart.

It is logical to assume that the left ventricle will fail first and that pulmonary edema will result, and indeed this is often the case. At first, there will be only dyspnea on exertion, then paroxysmal nocturnal dyspnea and finally persistent chronic pulmonary edema or bouts of acute pulmonary edema requiring emergency therapy.

It is possible, however, for right ventricular failure to occur and even predominate with the appearance of peripheral edema, high venous pressure and an enlarged liver. The reasons for this are not completely understood, but there are several possible explanations which probably operate in concert to produce the right ventricular failure. First, it should be recalled that the myocardial musculature is a syncytium involving both ventricles Damage to the major or left ventricle can compromise the weaker or right ventricle, although the reverse seldom occurs Second, the reduction of left ventricular output lowers the driving force that keeps the blood circulating and results in a tendency for blood to collect on the venous side of the circulation. Third, reduction of arterial pressure secondary to the fall of cardiac output stimulates the aortic and carotid sinus nerves to produce peripheral vasoconstriction involving postarteriolar as well as arteriolar small vessels. By this means, much of the blood normally distributed in the small vessels is shunted into the central venous system where it tends to accumulate because of the ineffective cardiac output Finally, the disordered circulation stimulates secondary reactions, possibly involving aldosterone secretion This may compromise salt and water excretion in the kidney, thus favoring salt retention and edema.

It seems probable, as pointed out a number of years ago on the sequence of events following severe myocardial infarction, that the body has only a limited number of response patterns to stress Indeed, most important for survival of the species are the reactions following hemorrhage; the wounded animal must fight or flee if he is to survive and propagate After hemorrhage, as the cardiac output falls, the baroreceptors are stimulated to constrict small

described an unusual instance of hypertension apparently due to thrombosis of a main branch of one renal artery. Approximately one-half of the kidney was supplied with low blood flow and pressure, the other with blood under high pressure. Histologic examination revealed hyperplastic arterioles on the hypertensive side and normal-appearing arterioles on the hypotensive side. Since the hypotensive side was not infarcted, it must have received some blood supply even though this was limited. Thus, if there were any unknown circulating or neurogenic toxic substance acting on arteriolar walls to damage them one would expect this factor to act on both portions of the kidney. Indeed, since the side distal to the thrombosed artery was the seat of the disorder, one would expect the arterioles to be, if anything, more diseased in that portion.

There is evidence to suggest that arteriolar smooth muscle, like the smooth muscle of the ureter or gastrointestinal tract, reacts to stretching by further contraction. Many years ago, Bayliss made this proposal, and more recently Folkow and others have shown that in vessels entirely freed of neurogenic or humoral influences elevation of pressure produce vascular constriction, while reduction of pressure induces peripheral vascular relaxation.[3] Teleologically, this intrinsic response of vascular smooth muscle provides a second line of defense in case of exhaustion or failure of the moderator (carotid sinus and aortic arch) reflexes. It also is important to note in this connection that the moderator reflexes in hypertensive individuals are set at a higher level. In addition, it is apparent that the constriction of smooth muscle to pressure provides a mechanism for the continuation of increased peripheral resistance even after the initiating cause of the hypertension has been removed. This may explain why hypertension sometimes fails to regress following removal of a pheochromocytoma, or a unilaterally diseased kidney, or following delivery in toxemia of pregnancy. Another important factor in the perpetuation of some hypertensions is the development of nephrosclerosis.

Accelerated Atherosclerosis of Large Arteries

Many of the incapacitating or fatal complications of hypertension are caused by the frequency of atherosclerosis of large arteries particularly in the cerebral and coronary blood vessels. The hypertensive patient is more prone to develop atherosclerosis than the normal individual. The incidence of myocardial infarction has been found to be four to five times higher in hypertensive males than in the general population and twenty times higher in hypertensive than in normotensive females.[4] It is well recognized also that the incidence of cerebrovascular atherosclerosis and thrombosis is unusually high in the hypertensive population.

Some factor must be present in the hypertensives which accelerates the atherosclerotic process. This acceleration may be due to the high pressure existing in the arterial tree or to some other unknown factor present in hypertensive patients. In deciding between these two possibilities, it is pertinent to refer to the changes that may occur in the pulmonary arteries following long-standing and persistent pulmonary hypertension. Pulmonary hypertension of long duration is found in certain forms of congenital heart disease, such as in patent ductus arteriosis with right-to-left shunt or in large interventricular septal defects in which the patients occasionally survive to adult life. The level of pulmonary pressure in such individuals is several fold higher than is normal for that system. At autopsy, it is common to find in such patients extensive atherosclerosis of the pulmonary rather than the systemic arterial system.

It is evident that if the acceleration of atherosclerosis were due to some circulating or neurogenic noxious factor it should affect *both* sides of the circulation. It would not spare the systemic circulation in pulmonary hypertension and the pulmonary circulation in systemic hypertension. The fact that the atherosclerosis is *limited* in each case to the areas of elevated pressure suggests strongly that the hypertension is the aggravating factor. These observations are not cited to imply that hypertension

In the intact animal or human,[4] the sequence of events appears to be as follows: As sympathetic vasoconstrictor discharges are inhibited by the blocking agent, some arteriolar dilation occurs which is followed quickly by postarteriolar (capillary and venular) relaxation and pooling of blood in these small vessels. As a result, right heart filling pressure declines due to lack of adequate venous return, and the cardiac output falls. Thus, there is produced a further fall in arterial pressure Since arteriolar relaxation and reduced cardiac output are present, the calculated total peripheral resistance relative to the cardiac output shows no significant change

In the presence of congestive heart failure, however, the cardiac output rises rather than falls after ganglion-blocking agents This paradoxical response results from the combined beneficial effects of arteriolar relaxation (decreased aortic pressure head reducing the work load) and pooling of blood volume peripherally (relief of central venous congestion).

The effects of the inhibition of the sympathetics are aggravated when the patient assumes the erect position (failure of compensatory reflex vasoconstriction) and are counteracted when he assumes the head down position, since gravity facilitates venous return Similarly, blood loss cannot be compensated for by vasoconstriction, and severe hypotension can result from only moderate depletions of total blood volume.[3] With continued inhibition of the sympathetics, however, some homeostasis seems to return in time. This so-called "autonomous tone" of the muscular blood vessels probably is due to the intrinsic property of smooth muscle to contract under stretch and to relax after the stretching force has been removed Normally, the sympathetic reflexes rather than autonomous tone provide the quick adjustments required for circulatory homeostasis during changes of body position. When the sympathetics no longer function effectively, as after surgical sympathectomy or ganglion-blocking drugs, the autonomous tone mechanism probably comes into play as a second line of defense

When the sympathetic tone is released, following ganglion-blocking agents there is also some redistribution of blood flow to the various areas of the body.[4] Renal blood flow is reduced at first, but, due to the remarkable autonomy of the renal vasculature, adjustments are made promptly to restore blood flow to control levels. Essentially, the same adjustment occurs in the brain. The hepatic-portal blood flow decreases whereas the flows of the calf and forearm increase immediately. In the hands and feet, however, if there has been vasoconstriction by, e g., placing the subject in a cold room, the increase in blood flow is approximately tenfold The other effects of ganglionic blockade are related to inhibited transmission of nervous impulses through all autonomic ganglia, parasympathetic as well as sympathetic

Salt-Restricted Diets and Saluretic Agents

Since it is our belief that low sodium diets and saluretic agents such as chlorothiazide produce similar hemodynamic effects, they will be discussed under the same heading The considerations are limited to the effects of diets, such as the rice diet, which are restricted to 200 mg of sodium per day or less It should be mentioned that diets more liberal in sodium content do not produce a degree of salt depletion necessary to induce a reduction of blood pressure

Salt depletion can be accomplished more effectively and quickly with a saluretic agent, such as chlorothiazide, than with a sodium-restricted diet If a nonedematous, hypertensive patient is given orally 1 0 to 1.5 Gm. of chlorothiazide per day, there will occur a prompt diuresis of sodium and chloride, and, to a lesser extent, potassium [5] During the first 48 to 72 hours, approximately 250 to 350 mEq. of sodium and chloride are lost from body stores, i.e., over and above the daily intake. If the chlorothiazide is maintained beyond this period, the depletion of body stores of salt levels off and the patient comes into balance with his intake. However, he does not regain the original losses If the salt ingestion is increased, the extra amount is excreted unless the intake is pushed to excessive levels (approximately 25 Gm. per day).

peripheral vessels of all types in order to shunt blood into the central circulation At the same time, the heart rate increases. In the healthy individual subjected to blood loss, these reactions are advantageous, but with a low output as in heart failure they only add to the burdens of an already overworked myocardium In addition, the reduction of cardiac output or possibly of arterial blood volume following hemorrhage or low output heart failure stimulates renal salt and water retention with resulting expansion of the extracellular fluid and plasma volumes. Within 48 hours following blood loss there develops a considerable expansion of plasma volume due to this mechanism Unfortunately, the body does not seem to differentiate between a reduction of cardiac output due to blood loss and a reduction due to cardiac failure The reaction which is so helpful to the rapid restoration of blood volume following hemorrhage only adds to the burdens of the failing heart producing edema and further venous congestion The salt and water retention mechanism restores blood volume and cardiac output in the healthy heart, thereby shutting off the stimulus to further salt retention. In the failing heart, however, as these burdens further reduce the cardiac output, the stimulus to salt and water retention increases, thereby setting up a vicious cycle

Other Complications

Dissecting aneurysm of the aorta which occurs almost exclusively in hypertensive patients may also be a direct consequence of the elevated pressure The aorta, being made up primarily of elastic tissue rather than smooth muscle, dilates in the presence of hypertension. It seems possible that the distention and stretching of the aortic wall may compromise the patency of the capillaries feeding the media and thus lead to medial necrosis. The resultant weakness of the aortic wall favors tearing or splitting in the presence of a constantly increased distending pressure or in a moment of extreme hypertensive overshoot. Very little is known about the mechanism of cerebral hemorrhage. It is recognized, however, that hypertension contributes to excessive bleeding during brain surgery.

These considerations as to the pathogenesis of the various organic complications of hypertension are of more than academic interest. If it is true that the elevated pressure produces organic damage, then reduction of blood pressure in the *early* stages of the disease would retard or prevent the development of organic damage The argument that effective antihypertensive therapy should be reserved only for the advanced patients who already have severe organic damage becomes illogical when viewed in the light of the basic considerations.

Pharmacology of Antihypertensive Agents

The basic mechanisms by which arterial pressure may be reduced are (1) by decreasing cardiac output and (2) by reducing total peripheral resistance. Most of the agents used today probably act on both mechanisms

Ganglionic Blocking Agents

The hemodynamic effects of the ganglion-blocking drugs can be demonstrated most clearly by substituting a mechanical pump for the left ventricle.[3] In an anesthetized dog, blood is diverted as it enters the left atrium into a reservoir and then is pumped back into the animal via a T tube in the descending thoracic aorta. When hexamethonium is injected intravenously, there is first a fall in arterial pressure, indicating clearly a decrease in peripheral vascular resistance, since the pump is maintained at a constant output There soon follows, however, a decrease in central venous pressure, pulmonary arterial pressure and a transient decrease in the volume of blood returned from the right heart through the pulmonary circulation to the reservoir. As a result of the temporary disparity between the output of the right heart and the pump's constant flow, the reservoir is depleted of several hundred milliliters of blood. Thus, the vascular volume or capacity of the dog must have increased sufficiently to accommodate the amount of blood transferred from the reservoir to the animal. Since this amount is too great to be explained on the basis of arteriolar dilation alone, it is apparent that the postarteriolar vessels must have dilated as well.

blood pressure of nonedematous normotensive or hypertensive subjects. It appears that a *depletion* of sodium ion induced either by diet or by potent saluretic agents reduces blood pressure in hypertensive patients. However, the hypotension occurs primarily because the salt loss is associated with a reduction of plasma *volume*. The unimportance of the sodium ion per se is indicated by the fact that the blood pressure can be restored simply by replenishing the plasma volume with salt-free dextran solutions. The role of salt, therefore, appears to be permissive. Its presence is required to maintain a normal expansion of plasma volume. This expansion permits normal vascular reactivity to the unknown pressor mechanism operative in hypertension. Salt loss and resulting plasma volume depletion reduce this vascular reactivity.

Hydralazine

Hydralazine or Apresoline produce hemodynamic effects which are unique among the antihypertensive agents. Pyrogenic substances produce similar hemodynamic changes, but hydralazine does not induce fever. Either hydralazine or pyrogenic substances produce a marked decrease in total peripheral vascular resistance while at the same time approximately doubling the cardiac output.[8] The heart rate also accelerates. Renal, splanchnic, cerebral and coronary blood flows increase, whereas flow remains essentially unchanged in the extremities.

Teleologically, the increased circulatory rate, particularly through the kidneys, heart and liver, aids in the rapid detoxification and elimination of noxious products associated with febrile infections and with the mobilization of body defenses. This represents another reaction pattern of the body useful for survival of the species which is advantageous in the treatment of hypertensive patients.

The increase in cardiac output counteracts the marked arteriolar relaxation induced by hydralazine, so that the percentage of fall in systolic pressure is not as great as the fall in diastolic. Therefore, when hydralazine is administered alone, the most significant reductions occur in the diastolic pressure. However, it is readily seen that if the venous return to the heart is impaired by the addition of ganglion-blocking agents or chlorothiazide the cardiac output cannot increase effectively, and the peripheral dilating effects of hydralazine then become relatively unopposed. For this reason, hydralazine is far more effective when used in combination with other drugs which reduce cardiac output, particularly chlorothiazide.

The tachycardia and palpitation produced by hydralazine sometimes is disturbing to the patient. If this is troublesome, Rauwolfia, which produces some bradycardia and also dulls apprehension, provides a worthwhile counteragent. In high dosages, hydralazine may produce a syndrome indistinguishable from disseminated lupus erythematosus. This does not occur, however, when dosages are maintained below 200 mg. per day. When properly administered, hydralazine is an extremely useful antihypertensive agent.

Other Antihypertensive Agents

Little is known about the hemodynamic effects of *Rauwolfia serpentina*. When injected parenterally in animals, reserpine, the active alkaloid of Rauwolfia, produces a central depression of sympathetic vasoconstrictor reflexes. When given orally in man, it is doubtful that the drug reduces basal blood pressure. It appears more likely that, following Rauwolfia, the patient becomes less emotionally reactive, and as a result the transient elevations of blood pressure caused by fear and apprehension become less frequent and severe. Since these elevations often occur as the result of subconscious or conscious fears associated with the visit to the doctor's office, Rauwolfia may give a false overestimation of antihypertensive potency when evaluated under such conditions. When evaluated under more critical conditions, notably in hospitalized patients, the drug in customary dosage has little if any antihypertensive effect on basal blood pressure.

The considerations of Rauwolfia are not meant to imply that the drug and its active alkaloid reserpine have no place in the treatment of hypertensive patients. By the parenteral route in dosages of 2 to 5 mg., reserpine is an active antihypertensive drug. By the oral route in far smaller dosages, it may be a useful

The *excreted salt* appears to be derived primarily from the total extracellular fluid space. The patient characteristically loses 1 to 2 kilos of body weight and 1 to 2 L of extracellular fluid as measured by thiocyanate, radiosodium or radiosulfate dilution spaces. The serum concentrations of sodium and chloride do not change significantly indicating that the elimination of extracellular salt and water is proportionate The serum concentration of potassium usually falls slightly, but this reduction frequently is progressive unless potassium supplements are administered

Included in the extracellular fluid space is the plasma volume which is reduced by about 15 per cent from its original level All of these effects occur approximately within the first 48 hours, during which time the blood pressure also falls The reduction in plasma volume and extracellular fluid space usually is maintained for periods of at least one month with the continued administration of chlorothiazide in the dosage of 500 mg. twice daily The hemodynamic importance of the plasma volume depletion is indicated by the fact that restoration of plasma volume loss alone, without added salt, as by infusion of 500 ml of 6 per cent dextran in glucose and water, usually returns the blood pressure to the previous or pretreatment level

Normotensive, nonedematous individuals also exhibit a similar saluretic response and reduction of extracellular fluid and plasma volumes However, unlike the hypertensive patients, there is no reduction of basal blood pressure. Nevertheless, altered vascular reactivity in that the degree of blood pressure elevation following infusions of pressor agents such as norepinephrine usually is reduced and the hypotensive response to depressor agents is increased. This altered vascular responsiveness can be reversed by restoring the plasma volume with salt-free dextran.

Several important considerations emerge from these observations First, there is a labile pool of extracellular fluid and plasma volume which can be eliminated either by effective saluretic agents or by severely restricted salt intake. Parenteral mercurials also produce a depletion of plasma volume with an alteration in vascular reactivity.

Second, the reduction of plasma volume alters vascular reactivity in both the normotensive and hypertensive individual but reduces basal blood pressure only in the hypertensive Our experience indicates that individuals with basal diastolic blood pressures in the region of 90 mm. Hg or above react to chlorothiazide with a fall of basal blood pressure, whereas those with diastolic levels of 85 or lower are not responsive Since the fall of blood pressure may occur even in patients with only mild elevations of diastolic blood pressure, it is concluded that a basic difference exists between mildly hypertensive and normotensive individuals We have interpreted our results to indicate that in all hypertensives, including those with only moderate elevations, a pressor mechanism or stimulus of some type is operative. Chlorothiazide reduces the blood pressure in such a group by decreasing the vascular reactivity to this stimulus

A third implication is that the studies show an important relationship between total blood volume and vascular reactivity It is probable that when the venous system is well filled a stimulus to vascular contraction produces a greater venous return to the heart than when the venous system is poorly filled According to Crosley and also Dunstan, the cardiac output in hypertensive patients is reduced by chlorothiazide It is a general property of muscle cells that the greater the initial tension the greater the contraction Thus, other things being equal, a decrease in blood volume would reduce vascular tone This reduction of vascular tone does not occur following hemorrhage, because the baroreceptor reflexes initiate sympathetic vasoconstriction, and the total blood volume is restored rapidly through hemodilution. Following chlorothiazide, however, these compensatory reactions are not prominent There is no tachycardia or other evidences of compensatory vasoconstriction in the hypertensive as contrasted to the normotensive subject after chlorthiazide

Finally, the studies of salt restriction and saluretic agents provide no evidence that sodium plays an important etiologic role in hypertension The effect of sodium seems to be secondary rather than primary, permissive rather than causative The administration of an *excessive* amount of salt does not elevate the

blood pressure of nonedematous normotensive or hypertensive subjects. It appears that a *depletion* of sodium ion induced either by diet or by potent saluretic agents reduces blood pressure in hypertensive patients. However, the hypotension occurs primarily because the salt loss is associated with a reduction of plasma volume. The unimportance of the sodium ion per se is indicated by the fact that the blood pressure can be restored simply by replenishing the plasma volume with salt-free dextran solutions. The role of salt, therefore, appears to be permissive. Its presence is required to maintain a normal expansion of plasma volume. This expansion permits normal vascular reactivity to the unknown pressor mechanism operative in hypertension. Salt loss and resulting plasma volume depletion reduce this vascular reactivity.

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adjunct in the total management of the patient *Psychic factors are important; certain* emotions, particularly fear (but probably not anger unassociated with fear) and anxiety, tend to oppose the antihypertensive effectiveness of most blood pressure-reducing drugs Reserpine is a particularly useful sedative in such patients. It should be mentioned, however, that the drug also is potentially harmful, since serious and long-lasting mental depressions as well as other disturbing side effects can occur following prolonged use. Therefore, it is safer to administer other sedative drugs, such as the barbiturates or meprobamate, whenever these will provide the desired psychic effects In regard to the so-called nonsedative, antihypertensive alkaloids of Rauwolfia, such as rescinnamine, when given orally in the advised dosages, this author has merely found a placebo-like action

The *Veratrum alkaloids* stimulate still another type of hemodynamic reaction pattern used by the body for survival This occurs when blood loss poses limitations for violent activity or when fear and other forms of psychic shock become overwhelming in the face of a challenge which cannot be met either by defense or flight In this situation, a sudden vasodilation occurs with a marked fall of blood pressure, the heart rate slows and the pulse becomes almost imperceptible, a deathly pallor ensues and consciousness is lost as the individual falls to the ground in a faint. This reaction is a prominent protective device of cold-blooded animals who affect all the appearances of death when caught in a position that permits no successful escape. In man, the residual of this reaction is called vagovagal syncope.

The efferent arm of the reflex response as mentioned above travels out over the vagus nerve to produce bradycardia and over unknown pathways to produce peripheral vasodilation The afferent arm may originate as follows: in the cortex under the impact of some intense emotional shock, in the carotid sinus or in afferent vagal nerve endings distributed to the lungs and myocardium. The Veratrum alkaloids *stimulate these afferent* nerve endings and so initiate a reflex vasodilation and bradycardia Syncope, however, rarely occurs, but nausea and vomiting, due to stimulation of the emetic center, is common. Thus, the drug does not entirely reproduce the picture of vagovagal syncope.

Of all known antihypertensive agents, the hemodynamic responses produced by the Veratrum alkaloids are the most physiologic. The cardiac output remains unchanged while the total peripheral resistance falls[7] Blood flowing to various body areas may fluctuate initially but soon reverts to the pretreatment level There is no interference with postural and other homeostatic reflex adjustments Unfortunately, Veratrum has been less satisfactory than other agents in long-term therapy for the following reasons. (1) a narrow spread between the hypotensive and the emetic dose and (2) the developement of tolerance to the antihypertensive effect.

Considerable progress has been made in the control of hypertension during the past 10 years and further advances are to be expected in the future Careful study of the mechanisms by which blood pressure can be reduced may continue to shed more light on the hypertensive process

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Pathophysiology of Acute and Chronic Pericarditis

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PERICARDITIS is an inflammation of the serous membranes surrounding the heart. The etiologic factors are listed in TABLE 1; primary pericarditis is rare Etiology, differential diagnosis and treatment will be considered only as they pertain to physiologic function. The following types of pericarditis will be distinguished. (1) acute fibrinous pericarditis (without significant effusion), (2) acute serofibrinous pericarditis (with effusion), (3) chronic constrictive pericarditis and (4) adhesive mediastinopericarditis.

ACUTE FIBRINOUS PERICARDITIS

Acute fibrinous pericarditis is usually a mild form of pericardial involvement, but it may become severe with the rapid development of adhesions and obliteration of the pericardial space It is encountered most frequently in acute rheumatic fever, tuberculosis, uremia and systemic lupus erythematosus

Pathology

The pathologic changes of fibrinous pericarditis consist of grossly visible roughened areas of the membranes, due to the deposition of fibrin In more serious cases, there is an accumulation of large, fibrinous tufts that give rise to a so-called "bread and butter" appearance of the pericardium There usually is a small amount of pericardial fluid, which may increase to 250 cc, causing a significant rise in intrapericardial pressure Healing results in complete absorption of the small exudate, but with the formation of whitish flat scars ("milk spots") or of adhesions of the two pericardial membranes or between the parietal membrane and adjacent structures.

Symptoms

The pain experienced in *acute pericarditis* is often attributed to actual involvement of the pericardium. It has been demonstrated, however, that the visceral membrane is free from pain fibers. The parietal membrane carries no pain fibers except in the lower part where they originate in the phrenic nerve This paucity of pain fibers explains the absence of pain in cases of acute pericarditis associated with uremia or acute myocardial infarction

When pain is present in acute pericarditis, it is usually caused by involvement of adjacent structures such as the pleura, the diaphragm and mediastinum. This is consistent with the exacerbation or provocation of the pain initiated by deep respiration and coughing, its frequently sharp character and radiation to the neck, shoulder or back.

An occasional symptom of alarming nature is *syncope*, occurring as the initial symptom; the mechanism is not clear. It is probably of reflex origin and provoked by the severity of the pain or by the irritation of the pericardium. Without careful differentiation an erroneous diagnosis of acute myocardial infarction may be made in such cases General symptoms of fever, chills, sweating, fatigue, etc. depend to a great extent on the etiologic factors responsible for the acute pericarditis.

Signs

The most common objective finding is the *friction rub.* The sound is more prolonged than any normal or adventitious heart sound even when limited to a single phase of the cardiac cycle. The frequency of the component vibrations is very high, usually in the range of 100

adjunct in the total management of the patient. Psychic factors are important, certain emotions, particularly fear (but probably not anger unassociated with fear) and anxiety, tend to oppose the antihypertensive effectiveness of most blood pressure-reducing drugs. Reserpine is a particularly useful sedative in such patients. It should be mentioned, however, that the drug also is potentially harmful, since serious and long-lasting mental depressions as well as other disturbing side effects can occur following prolonged use. Therefore, it is safer to administer other sedative drugs, such as the barbiturates or meprobamate, whenever these will provide the desired psychic effects. In regard to the so-called nonsedative, antihypertensive alkaloids of Rauwolfia, such as rescinnamine, when given orally in the advised dosages, this author has merely found a placebo-like action

The *Veratrum alkaloids* stimulate still another type of hemodynamic reaction pattern used by the body for survival This occurs when blood loss poses limitations for violent activity or when fear and other forms of psychic shock become overwhelming in the face of a challenge which cannot be met either by defense or flight In this situation, a sudden vasodilation occurs with a marked fall of blood pressure, the heart rate slows and the pulse becomes almost imperceptible, a deathly pallor ensues and consciousness is lost as the individual falls to the ground in a faint This reaction is a prominent protective device of cold-blooded animals who affect all the appearances of *death when caught in a position that permits* no successful escape. In man, the residual of this reaction is called vagovagal syncope

The efferent arm of the reflex response as mentioned above travels out over the vagus nerve to produce bradycardia and over unknown pathways to produce peripheral vasodilation The afferent arm may originate as follows: in the cortex under the impact of some intense emotional shock, in the carotid sinus or in afferent vagal nerve endings distributed to the lungs and myocardium. The Veratrum alkaloids stimulate these afferent nerve endings and so initiate a reflex vasodilation and bradycardia. Syncope, however, rarely occurs, but nausea and vomiting, due to stimulation of the emetic center, is common. Thus, the drug does not entirely reproduce the picture of vagovagal syncope.

Of all known antihypertensive agents, the hemodynamic responses produced by the Veratrum alkaloids are the most physiologic. The cardiac output remains unchanged while the total peripheral resistance falls.[7] Blood flowing to various body areas may fluctuate initially but soon reverts to the pretreatment level There is no interference with postural and other homeostatic reflex adjustments. Unfortunately, Veratrum has been less satisfactory than other agents in long-term therapy for the following reasons: (1) a narrow spread between the hypotensive and the emetic dose and (2) the developement of tolerance to the antihypertensive effect.

Considerable progress has been made in the control of hypertension during the past 10 years and further advances are to be expected in the future. Careful study of the mechanisms by which blood pressure can be reduced may continue to shed more light on the hypertensive process

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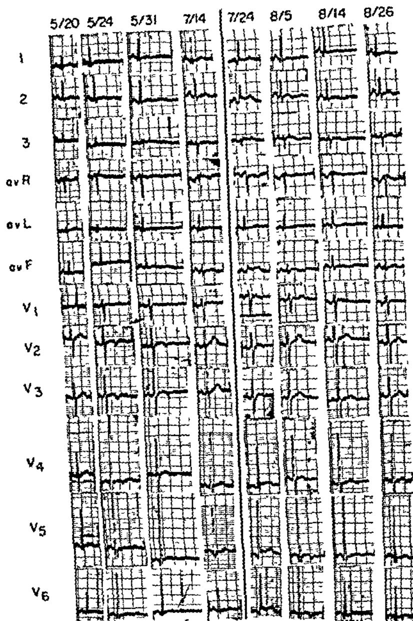


FIG 1 —Serial electrocardiograms obtained during 2 episodes (5-20 and 7-21) of recurrent nonspecific (benign idiopathic) pericarditis reveal progressive S-T and T wave changes Note, however, the variable configuration of the S-T segment Also, the extensive involvement of the pericardium following the second attack leads to S-T elevation in most leads and reciprocal S-T depression in avR

ment, or it may be present in only two of the standard limb leads and in a variable number of the precordial leads This depends on the extent of the pericardial involvement and the spatial relationship of the electrodes to the involved area Therefore, the findings of a reciprocal depression of the S-T segment in some leads should not be used for the differentiation of acute pericarditis and acute myocardial infarction, only the presence of pathologic Q waves offers conclusive evidence of the latter condition

The T waves usually undergo a gradual change from low amplitude and notching to isoelectricity and ultimate inversion. The inverted T wave phase lasts longer than that of the S-T changes It may persist for several months after complete clinical recovery has oc-

TABLE 1.—*A Classification of Diseases of the Pericardium**

ACUTE (AND SUBACUTE) DISORDERS

Acute nonspecific (benign idiopathic) pericarditis
- primary
- postcommissurotomy
- postmyocardial infarction syndrome (Dressler)

Pericarditis due to living agents
- tuberculous
- purulent (pyogenic)
  - pneumococcal — tularemic
  - streptococcal — meningococcal
  - staphylococcal — secondary to hepatic or subphrenic abscess
  - Neisserian
  - Friedlander — hemophilus influenzae
- protozoal
  - echinococcal — amebic
  - Necator americanus
- mycotic
  - actinomycosis — coccidioidomycosis
- viral (?), e g , mumps (?), lymphopathia venereum, infectious mononucleosis, Coxsackie virus

Connective tissue disorders and allergic diseases
- rheumatic fever
- systemic lupus erythematosus
- allergic granulomatosis
- rheumatoid arthritis
- serum sickness

Chemical or metabolic
- uremia
- diabetic acidosis
- Addison's disease
- myxedema

Neoplastic
- primary
- metastatic
- lymphomatous, e g , Hodgkin's disease
- leukemic

Pericarditis secondary to abnormalities of heart and great vessels
- with mycardial infarction
- with coronary embolism
- with dissecting aneurysm of the great vessels
- with bacterial endocarditis

Pericarditis with a physical basis
1. trauma
2. x-ray

CHRONIC DISORDERS OF PERICARDIUM

Chronic constrictive pericarditis
Chronic mediastinopericarditis
Chronic pericardial effusion
- myxedema
- cholesterol pericarditis
- chylopericardium
- anemia
- ? trauma
- chronic idiopathic pericardial effusion

TABLE 1.—*Continued*

Pericardial cyst and diverticulum
Congenital absence of pericardium

* Modified after McKUSICK, V. A , Advances Int Med 7 158, 1955

to 300 cps with an intensity that is slight to moderate

A pericardial friction rub differs from a cardiac murmur in that it is best heard with the patient in the upright position; intensity can be accentuated by pressing the chest piece of the stethoscope against the chest immediately over the precordium.

A friction rub is noted not only during the attack of dry fibrinous pericarditis but also after the development of pericardial effusion There is striking variation in the incidence of pericardial rubs, their location and extent, duration and intensity Friction rubs may vary with the position of the patient and the phase of respiration The "rub" is produced by the friction induced by rubbing of the fibrinous surfaces of the two pericardial membranes, and its variability is related to the location and extent of the morphologic changes of the pericardium

Laboratory Findings

The electrocardiogram shows significant changes in all but the mildest episodes of acute pericarditis. The abnormalities involve mainly the S-T segment and the T wave (FIG 1) In rare instances, there is present an electrical alternans, even in the absence of any other demonstrable myocardial involvement.

The S-T segment change is the most consistent It occurs early and tends to disappear before the occurrence of T wave changes The elevated S-T segment exhibits either a straight oblique course upward to the peak of the T wave or retains the upward concavity of a normal S-T segment The S-T segment may also show the upward convexity which is noted, however, more commonly in acute myocardial infarction This usually occurs at the time the T wave becomes inverted. The S-T elevation persists for a variable period, usually about one week It is found in all limb and precordial leads with the exception of AVR where there is usually reciprocal depression of the S-T seg-

(or postcardiotomy syndrome). It has been suggested that nonspecific pericarditis actually may be an expression of rheumatic or allergic hypersensitivity of the pericardium. A similar type of pericarditis has been described recently following acute myocardial infarction.[18]

Acute Serofibrinous Pericarditis (with Effusion)

This form of pericarditis is characterized by the presence of variable amounts of fluid in the pericardial sac in addition to the fibrinous changes of the membranes. The fluid may be serous, serosanguineous or distinctly hemorrhagic, and at times purulent. This type of pericarditis is caused by and large by the same agents responsible for the fibrinous type of pericarditis.

Physiologic Changes

Rapid accumulation of even small amounts of fluid may lead to severe disturbances with alarming signs and symptoms. There is an increase in intrapericardial pressure which interferes with the filling of the right atrium and ventricle. Inflow stasis ensues with increased pressure in the right ventricle, the right atrium and large veins. As the result of this inflow stasis the neck veins fail to collapse normally during the inspiratory phase.

Large effusions may also interfere with the emptying of the cerebral veins. This accounts for cerebral symptoms of dizziness or fainting. The hepatic veins often show an early increase in pressure secondary to the rise in intrapericardial pressure, or directly because of compression by the large pericardial effusion.

The presence of a large pericardial effusion is often associated with orthopnea and dyspnea, but the orthopnea differs from the orthopnea of left ventricular failure. There is probably a degree of compression of the lung with resultant atelectasis. The upright position does not give prompt relief as would be expected in left ventricular failure, and frequently patients will lean forward or assume the knee-chest position. Compression of the esophagus by a large pericardial effusion is responsible for dysphagia. Pressure on the recurrent laryngeal nerve may cause ...

With excessive increase of the intrapericardial pressure extreme manifestations may occur, as characterized by a diminished venous return with resultant reduction of the stroke volume and a lowered pulse pressure. This is called *cardiac tamponade* and represents a life-threatening situation. The hemodynamic changes have been duplicated under experimental conditions.

Another phenomenon observed not infrequently in patients with large pericardial effusions is the *pulsus paradoxus*. It consists of a marked reduction of the pulse amplitude and blood pressure during inspiration. Normally, a slight drop in blood pressure occurs during inspiration, amounting to less than 10 mm. The pulsus paradoxus is, however, not specific for pericardial effusion. It may be found in respiratory disorders such as bronchial asthma and bronchial stenosis associated with an excessive increase of negative intrathoracic pressure during the inspiratory phase. Even a large pleural effusion may cause a paradoxical pulse. Observation of the neck veins may be helpful in the differentiation of pericardial disturbances and respiratory causes of the pulsus paradoxus. Where the pericardium is the cause, the neck veins appear filled during the inspiratory phase, but if the cause is respiratory, they collapse on inspiration.

Symptoms

The symptoms of serofibrinous pericarditis depend mainly on the amount and rate of accumulation of the pericardial effusion. In addition to the pain noted in dry, fibrinous pericarditis there is a dull oppressive discomfort, related to the distention of the pericardial sac.

Orthopnea and dyspnea are frequently associated with large or rapidly accumulating effusions and are most likely caused by the diminished vital capacity secondary to pulmonary compression. Cough, hoarseness and dysphagia may result from compression of adjacent structures by the pericardial effusion.

Objective Signs

The objective features depend upon the hemodynamic disturbances and the compression of adjacent structures caused by the pericar-

curred. The late changes in the T wave are usually characterized by peaking and deep inversion

The *electrophysiologic mechanism* of the S-T and T changes is related *to the injury of the* subepicardial layers of the myocardium which occurs in acute pericarditis The mechanism of the persistent deep T wave inversion is not well understood A change of the QRS and T voltage occurs in instances of massive pericardial effusion or where thick masses of fibrin are deposited and constrictive pericarditis ensues

Acute Nonspecific Phase Reactants

Of the nonspecific indicators of inflammation, the erythrocyte sedimentation rate and white blood cell count tend to be abnormally elevated in many cases, the sedimentation rate more frequently so than the white blood count. The latter may be abnormally low in some cases

Among the more recently employed nonspecific phase reactants *C-reactive protein* (CRP) and the *plasma fibrinogen concentration* have been observed serially in acute rheumatic, acute nonspecific and presumptive tuberculous *pericarditis They yield abnormal findings in a* high percentage of the cases, usually in the most severe forms In general, however, they behave erratically.

The *antistreptolysin-O titer* (ASO titer) is of limited value It is frequently elevated in acute rheumatic pericarditis, particularly, in childhood and adolescence, but is usually normal in adulthood. It is rarely elevated in acute nonspecific pericarditis

The Fibrinogen Polymerization Test

The *fibrinogen polymerization* (FP) *test* of Losner and Volk was found originally to be more specific for the diagnosis of acute rheumatic fever and rheumatoid arthritis than the above-discussed acute phase reactants. It is based on *the observation that critical amounts* of heparin added to freshly drawn blood accelerate the polymerization of fibrinogen in acute rheumatic fever. Such a "positive" test was also observed in acute rheumatic and nonspecific pericarditis The FP test offers an additional advantage since it is not promptly suppressed by salicylates or steroids in contrast to the nonspecific acute phase reactants. It reflects faithfully the duration of activity of the disease process.

Particular Forms of Fibrinous Pericarditis

In *acute rheumatic fever* microscopic evidence of pericardial involvement is nearly always present in the fatal cases while clinical manifestations are reported in only a small percentage of patients The pericarditis is commonly seriously associated with acute myocardial involvement and may lead to the formation of adhesions between the visceral and parietal membranes or between the latter and mediastinal structures

Tuberculosis may cause a *fibrinous pericarditis* with a small amount of effusion, but large amounts of fibrin and the rapid development of partial or complete obliteration of the pericardial space result in chronic constrictive pericarditis Further extensions involving the adjacent mediastinum or pleura frequently eventuate in adhesive mediastinopericarditis or pleuropericarditis

Uremic pericarditis tends to be of the dry, fibrinous type, but even large effusions may occur *The condition is usually associated* with the terminal phase of renal lesions. With recovery recurrent pericarditis, complete healing and the formation of adhesions have been observed Metabolic chemical alterations have been incriminated in this type of pericarditis

Disseminated lupus erythematosus frequently causes pericardial involvement It appears in one-half of the cases and at times as the first clinical manifestation It is occasionally associated with large effusion, but most commonly is of the dry, fibrinous type Recurrences are not uncommon

Acute, nonspecific (benign idiopathic) pericarditis is probably the most common type of pericarditis encountered in adulthood It occurs also with sufficient frequency in adolescence *and childhood to warrant* differential diagnostic consideration It appears frequently, in the wake of upper respiratory infections, and has a marked tendency to relapse It is often accompanied by pneumonitis and pleuritis The clinical course resembles closely that of rheu*matic and tuberculous pericarditis*, and also pericarditis complicating surgery of the heart

(or postcardiotomy syndrome). It has been suggested that nonspecific pericarditis actually may be an expression of rheumatic or allergic hypersensitivity of the pericardium. A similar type of pericarditis has been described recently following acute myocardial infarction [15]

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ness with a flat percussion note over the precordial area suggests the presence of pericardial effusion. The area of dullness below the angle of the left scapula which may extend considerably over the left lower scapula posteriorly (Ewart's or Pin's sign) is related to the compression of the lung and resultant atelectasis. A dull percussion note is usually found in the fifth right intercostal space parasternally (Roche's sign). The apex beat may be diminished or absent, at times, it persists even in the presence of massive effusions. It is often felt inside the left border of cardiac dullness.

Auscultation may reveal a friction rub in spite of the demonstrable presence of pericardial effusion. The heart sounds are usually audible, but faintness occurs as fluid accumulates.

In summary, the neck vein distention with the lack of inspiratory collapse, the pulsus paradoxus, the decrease in pulse pressure, the large liver and ascites are striking features of hemodynamic alterations. Increased venous pressure with a concomitant drop in systolic and pulse pressure is significant in the consideration of threatening cardiac tamponade.

Laboratory Features

The *electrocardiogram* often shows, in addition to the S-T and T wave changes occurring in fibrinous pericarditis, a diminution of the voltage of QRS and T. This may be due to the short circuiting of the current by the large fluid mass.

X-ray Features

The normally sharp outline of the cardiac segments is usually obliterated, as best noted in the region of the pulmonic artery segment. This results in a pear-shaped or water bottle appearance of the cardiac silhouette. There is also a widening of the supracardiac vascular area, and a bulge may appear in the posterior and inferior area of the cardiac silhouette seen in the right anterior oblique view. Fluoroscopy frequently reveals a marked reduction or complete absence of cardiac pulsations ("quiet heart").

Angiocardiographic studies reveal a normal-sized heart opacified by the contrast medium and the surrounding pericardial fluid. In lateral projection, the fluid always appears anterior, retrosternal and infracardiac while displacing the heart posteriorly; small amounts of fluid apparently accumulate first below the heart. With massive accumulation of fluid, the lateral processes of the pericardial sac fill and extend laterally. Angiocardiography appears useful, for accurate diagnosis in doubtful cases (FIG. 2A AND B).

Laboratory procedures. The acute nonspecific phase reactants and the fibrinogen polymerization test behave in serofibrinous pericarditis essentially as they do in dry, fibrinous pericarditis.

Additional Diagnostic Procedures

Pericardiocentesis may be required for the differential diagnosis of pericardial effusion and cardiac dilatation. In either case, this procedure is not without risk, for an enlarged and dilated heart may be easily lacerated. The danger, however, is less with normal or hypertrophied hearts, but inadvertent puncture of the ventricle or a coronary artery is *still possible*. The margin of safety is extended by connecting the base of the exploring needle with a unipolar chest electrode. Thus, elevation of the S-T segment will indicate contact of the needle with the epicardial surface of the ventricle. Since angiocardiography has demonstrated the localization of *small* amounts of pericardial effusion below the heart, the subxiphoid approach recommended by Marfan for pericardial tapping appears not only safest but also most likely to yield fluid.

Pericardial tapping may also be utilized for determination of the *intrapericardial pressure* (FIG. 2 D–F). It will be found markedly elevated in cardiac tamponade. A satisfactory drop may be demonstrated as the patient is relieved following removal of an adequate amount of fluid. The diagnostic value of the pericardial tap can be enhanced significantly by the *instillation of air* following withdrawal of some fluid. This permits evaluation of the heart size, the thickness of the parietal pericardium and the presence of adhesions. An induced pneumopericardium may have some therapeutic value and prevent the development of constrictive pericarditis; caution is essential.



FIG 2 —(A) Erect teleroentgenangiocardiogram, demonstrating the cardiovascular system in pericardial effusion Frontal view shows that the superior vena cava and inferior vena cava are normal in size, configuration and location The right atrium, right ventricle and pulmonary artery are also normal Note the pericardial fluid surrounding the right heart structures Arrow points to the diaphragmatic border of the right ventricle (Courtesy of Dr I. Steinberg)

Examination of the pericardial fluid may yield valuable information. A purulent character suggests pyogenic pericarditis A hemorrhagic effusion is perhaps most frequently noted in tuberculous and neoplastic pericarditis It may also be found in myocardial infarctions, in rheumatic, uremic and post-traumatic pericarditis Culture and animal inoculation of the fluid may be helpful in suspected cases of tuberculosis.

Another method useful for the differentiation of cardiac dilatation and pericardial effusion is *cardiac catheterization*. Contact of the catheter with the right atrial wall and the relation of this point to the right lung field may establish the presence or absence of pericardial

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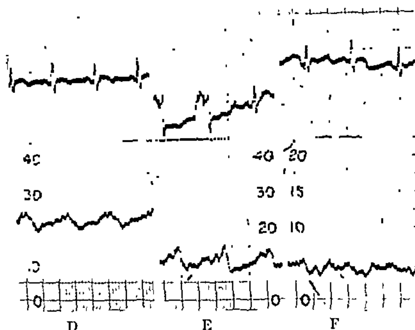


FIG. 2. (D, E, F)—Intrapericardial pressures obtained in massive pericardial effusion before (D) and after repeat withdrawal (E and F) of pericardial fluid. The pressure dropped from an initial average 23 mm Hg to a final average of 3.5 mm Hg. This coincided with marked subjective relief of the patient and markedly reduced engorgement of his neck veins.

effusion. Thoughtful consultation is essential before undertaking this procedure.

Constrictive Pericarditis

The two most important chronic disorders of the pericardium are constrictive and adhesive pericarditis or mediastinopericarditis. Since the term pericarditis implies an inflammation, its use is justifiable only in the occasional case of pericardial constriction occurring during the inflammatory stage of tuberculosis. Usually, the constrictive lesions of the pericardium represent the sequelae of the previous acute pericarditis. The term concretio cordis is, therefore, more appropriate for the description of a disease characterized by scar tissue formations, enveloping the heart in a constricting manner.

The etiology of constrictive pericarditis includes tuberculosis, pyogenic infection, rheumatic fever and trauma; the etiology remains obscure in many cases.

Pathology

The pathologic findings consist of layers of fibrous tissue of variable thickness and toughness, usually with complete hyalinization. A variable amount of calcium may be deposited either in patchy form or contiguously over wide areas, sometimes encircling the heart as a shell. The pericardial space may be completely obliterated. Where the line of cleavage between the original visceral and parietal membranes is still detectable, loculated serosanguineous fluid, pus or caseous debris may be found, also in small pockets within the dense scar tissue. The extent and type of scar formations vary from band and plaque-like lesions to a complete envelope of constrictive fibrous and calcified tissue. This involves not only the heart itself but at times also the venae cavae and even the hepatic veins. The latter is the usual finding in *polyserositis or Concato's disease*, a type of serofibrinous pericarditis associated with pleuritis and peritonitis and leading to progressive thickening of the pericardium and ultimate constriction.

In long-standing cases, the myocardium becomes markedly atrophic. The liver shows severe fibrosis, both central and portal in location, and in some instances severe intimal thickening and thrombosis of the hepatic vein.

Physiologic Changes

The basic physiologic disturbance responsible for the clinical manifestations and the relentless downhill course of constrictive pericarditis, especially when untreated, involves the diastolic filling and systolic output of the heart and, secondarily, disturbances of the systemic and

Fig 2 —(B) The left atrium with its venous channels is opacified The left ventricle and the aorta are also revealed Arrow points to the diaphragmatic border of the left ventricle Again note the fluid surrounding the left heart. (Courtesy of Dr I Steinberg) (C) Left lateral projection, showing the opacified right heart structures Note the hugh retrosternal and infracardiac pericardial effusion (Courtesy of Dr I Steinberg)

venae cavae and right atrial pressures, and between the mean right atrial pressure and the right ventricular diastolic pressure. The right ventricular pressure curve shows a characteristic early diastolic dip followed by a diastolic plateau The pressure at this "plateau" usually exceeds one-third of the ventricular systolic pressure. This pattern is due to restriction of ventricular filling which begins early in diastole and persists through the remainder of this phase

The pulmonary artery wedge (pulmonary "capillary" pressure) is usually elevated to the same degree as the pulmonary arterial diastolic, right ventricular end-diastolic and mean right atrial pressures The pulmonary artery wedge pressure usually remains below the level at which pulmonary edema is observed It never reaches values seen in mitral stenosis or left ventricular failure, even after exercise. This is probably due to the impaired output of the right ventricle, which explains the rarity of severe paroxysmal dyspnea or sudden pulmonary edema in patients with constrictive pericarditis

Determination of the stroke volume and cardiac output in mild cases reveals normal resting values, but, in many cases, the cardiac output fails to rise in response to exercise or saline infusion. In more severe cases at rest, abnormally low values may be found.

The abnormalities in cardiodynamics discovered by cardiac catheterization usually correlate with the findings obtained by *electrokymography* (Fig. 5). The cardiac borders and movements are revealed as follows: (1) a very rapid (steep) filling phase of the ventricle; (2) an abrupt arrest of this phase early in diastole and (3) no further filling during the remainder of diastole. The normally present indentations of the ventricular electrokymogram corresponding to the isometric relaxation and contraction are missing in constrictive pericarditis so that tracings of the ventricular border present a so-called "flat-top and V" pattern.

Phonocardiographic records reveal frequently the acoustical manifestations of the dynamic disturbance of diastolic filling An adventitious sound can be demonstrated early in diastole prior to the point in this phase at which the third sound is usually found. This protodiastolic sound of constrictive pericarditis is generally of slightly higher pitch than the protodiastolic gallop sound, and it occurs toward the end of the rapid filling phase (Fig. 6)

A *graphic tracing* of the pulsations in the precordial or apical region (kinetocardiogram) frequently shows a systolic negative deflection

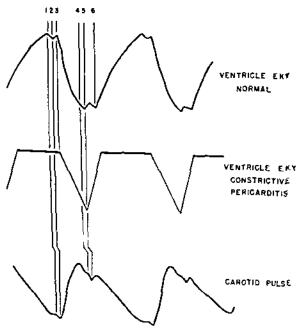


Fig 5—A schematic representation of the normal ventricular border electrokymogram and the "flat-top and V" electrokymogram of constrictive pericarditis with carotid pulse tracing for timing purposes Phases of cardiac cycle 1–2, isometric contraction; 2–3, early ejection, 4–5, late ejection ("[illegible]
M[illegible]
B[illegible]

pulmonary veins The normal diastolic relaxation of the heart is impaired by the dense pericardial scar with resultant reduction of venous inflow The earlier concept that constrictive pericarditis results from constriction of the venae cavae on entering the atrium is no longer tenable.

Experimental production of localized constriction has revealed the following situations (1) constriction of the right atrium has no untoward effect, (2) constriction of the right ventricle results in ascites hepatomegaly and increased systemic venous pressure, (3) constriction of the left ventricle results in pulmonary congestion, (4) total constriction causes a combination of dynamic alterations; and (5) the effects of total constriction cannot be relieved merely by freeing the right atrium. These experimental findings agree with clinical studies and hemodynamic measurements in man

With *cardiac catheterization* (Figs 3 and 4) there usually is a normal gradient between the

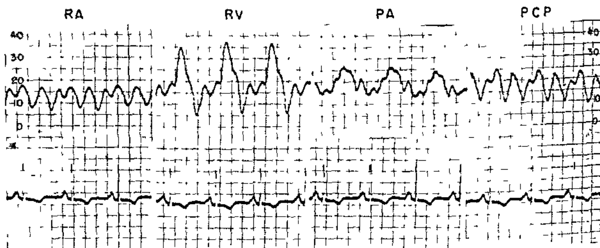


Fig 3 —Constrictive pericarditis The configuration of intracardiac pressure curves shows the frequently observed M shaped pattern in the right atrium (RA) and the early diastolic dip followed by a diastolic elevation in the right ventricle (RV) The mean right atrial, the right ventricular diastolic, pulmonary arterial diastolic and mean pulmonary artery wedge (pulmonary "capillary") pressures are all elevated and lie within a narrow range (14, 16, 15 and 17 mm Hg, respectively) The right ventricular systolic pressure is higher than the pulmonary arterial systolic pressure because the pressure tracings shown here were not all obtained in immediate time sequence

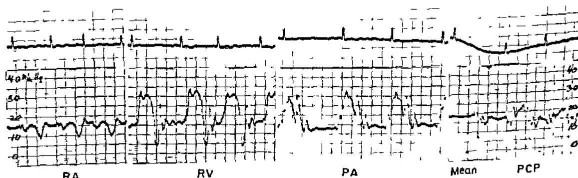


Fig 4 —Constrictive pericarditis The configuration of intracardiac pressure curves shows a [illegible]

[illegible] lary) pressures are elevated and all lie within a narrow range (17, 16, 14 and 18 mm Hg, respectively) The pulmonary arterial and right ventricular systolic pressures are slightly above normal.

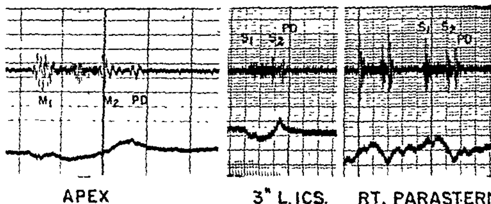


FIG 7 —R H , 57 years old Constrictive and adhesive pericarditis (confirmed by autops
ations from the ch
" L ICS) demonstr
er coincides with t
protodiastolic sound (PD) In contrast, there is systolic elevation followed by diastolic retr
tion in the right parasternal region The apex tracings are recorded at a paper speed of 75 mn
second, others at 25 mm /second (Dr W Dressler kindly permitted examination of tl
patient)

docarditis are particularly striking examples. Severe myocardial fibrosis due to coronary artery disease may also simulate constrictive pericarditis

Constrictive pericarditis is occasionally accompanied by constrictive pleuritis The latter reduces pulmonary ventilation and thoracic expansion and thus becomes responsible for a reduced vital capacity and resultant dyspnea

Symptoms

The symptoms experienced by the patient are directly attributable to the underlying dynamic disturbances. Thus, the most common complaint of abdominal swelling and associated discomfort is related to the ascites and hepatomegaly The dyspnea which may be present at first only on exertion is related to the failure of the cardiac output. If dyspnea occurs at rest it may be due to pulmonary congestion or a large pleural effusion. It may also be caused by the reduced vital capacity secondary to the elevation of the diaphragm by large amounts of ascites Fatigability and weakness are probably related to the reduced cardiac output

Clinical Signs

The various signs encountered in constrictive pericarditis can be explained adequately on the basis of the observed disturbance of cardiodynamics *Inspection* frequently reveal
neck veins with slight edema and c
the face and neck (Stokes' collar),
impulse tends to be absent In man
systolic retractile movement may be
the left precordial area. An early dia
ward rebound in the apical or precor
may follow or become associated wi
retraction

Palpation may demonstrate the s
traction, the early diastolic heave ov
midprecordial area and the pulsus p
The *systolic retraction and diastolic*
represented graphically by the rec
precordial pulsations (FIG 7). A pu
doxus is found in most cases of co
pericarditis. Its mechanism is essen
same as in massive pericardial effus

Percussion may reveal a heart of
increased size The latter is usually d
vious myocarditis or an intrinsic m
or endocardial condition.

Auscultation reveals as the most con
striking finding an adventitious prot
sound In some instances a presysto
may be noted This is related to the
atrial pressure as is the atrial gallop
congestive heart failure. The first ar
sounds usually are diminished in int
may be reduplicated The second

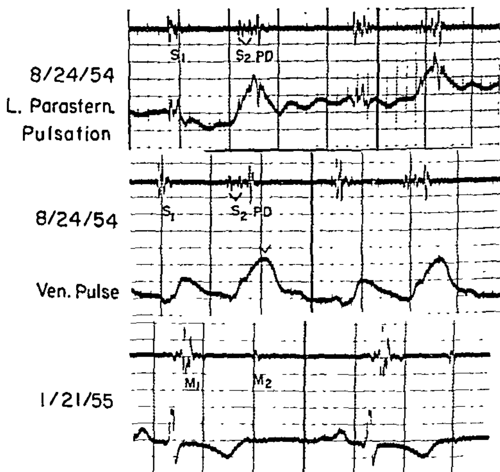


FIG 6 —Tracings on 8/24/54 were obtained from a patient with constrictive pericarditis and mitral stenosis before cardiolysis *Top tracing* shows a reduplicated first (S_1) and second sound (S_2) and the protodiastolic sound (PD) characteristic of constrictive pericarditis Note the systolic depression and early diastolic elevation of the precordium recorded by the linear phonocardiographic method Note the close relation of the sound PD to the early diastolic rebound *Middle tracing* demonstrates the time relationship of this sound to the V wave of the venous pulse recording *Bottom tracing* (obtained after successful cardiolysis) The reduplication of the first and second sound and the protodiastolic sound have disappeared The phonocardiogram reveals the delayed onset and prominent of the first sound consistent with mitral stenosis

followed by a diastolic positive deflection The latter coincides with the protodiastolic sound (FIGS. 6 AND 7) and can also be found in ballistocardiograms The systolic retraction is probably due to the effect of adhesions on normal variations in the shape and position of the heart during systole

The alterations of the *peripheral circulatory dynamics* consist of an early rise of the systemic as well as the pulmonic venous pressure. The persistence of venous hypertension in the presence of a reduced cardiac output is possible only if there is an increase of the circulating blood volume This results from the disturbance of renal blood flow and the resultant salt and water retention, as in congestive heart failure. Experimental data obtained in dogs with induced constrictive pericarditis suggest that altered adrenocortical function may also be responsible for the development of edema and ascites The increased circulating blood volume causes marked congestion of the venous system, hepatomegaly, generalized edema and ascites, and the pulmonary congestion.

Dynamic disturbances closely resembling those of constrictive pericarditis may be caused by myocardial disease. Primary systemic amyloidosis and Loeffler's fibroplastic parietal en-

Treatment

Medical treatment may lead to considerable improvement even before surgical intervention, especially cardiac tamponade due to recurrent intrapericardial effusion superimposed upon mild or moderate constrictive pericarditis. Procedures have been discussed previously. The clinical improvement may be correlated with the changes in cardiac output and the index obtained by serial cardiac catheterization.

The definitive treatment of constrictive pericarditis concerns the surgical removal of the compressing scar tissue. In the successful operations, there is marked improvement and even complete disappearance of the dynamic disturbances caused by the constrictive process.

The extent of the surgical *decortication* is somewhat controversial. However, the consensus of opinion suggests that the surface of the left and right ventricle should be freed to provide an adequate release and that decortication of the atria and venae cavae may be unnecessary. The procedure is not always feasible because of the danger of incising thin walls of the atria and venae cavae. Also, it may be impossible to free the posterior and diaphragmatic surfaces of the ventricles due to inaccessibility of these regions. Fortunately, the procedure may be unnecessary.

Freeing the apex and anterior surface of the ventricles results in adequate filling and emptying of these chambers. This may be proved through gross inspection of the heart as it herniates in the pericardial defect during operation, and also by noting the resultant increase of the systolic and pulse pressure. Postoperative cardiac catheterization reveals, in successful cases, a drop of the left atrial, right ventricular and pulmonary artery pressures, and a rise of the stroke volume and cardiac index.

An important aspect at operation is the sequence of decortication. The left ventricle must be freed first so that the chamber may receive the increased inflow load following release of the right ventricular compression, otherwise sudden left ventricular failure and even fatal pulmonary edema may occur. In long-standing cases with considerable atrophy, cardiolysis is fraught with great danger, death may occur during or shortly after the procedure. The suddenly decompressed chamber, usually the left ventricle, may dilate, eventuating in severe, rapidly-progressive failure. Surgical intervention in diagnosed cases, at the earliest possible date, is important.

The changes of venous congestion and its sequelae postoperatively improve with variable speed. In some cases, this is quite rapid; in others, the improvement occurs slowly over a period of several months.

Adhesive or Mediastinopericarditis

The condition known as adhesive pericarditis or accretio cordis is characterized by the presence of adhesions between the pericardium and neighboring structures, usually the mediastinum. It is frequently associated with constrictive pericarditis. The most common etiologic factor is rheumatic fever, valvular lesions of the heart are noted not infrequently.

The altered cardiodynamics encountered in the isolated form have been ascribed to the fixation of the heart with the anterior chest wall, the ribs, the lungs, the diaphragm and even the spine. This results presumably in an increased work load of the heart with resultant cardiac enlargement and failure, adhesions between the pericardium and the ribs are considered primarily responsible for this dynamic disturbance. However, there is considerable doubt as to the validity of this explanation. The increased cardiac size can usually be correlated with the presence of valvular or vascular heart disease. Indeed, the other cardiodynamic alterations and their clinical manifestations ascribed to the external adhesive process are identical with those seen in constrictive pericarditis (Fig. 7).

There are few signs specifically related to the external adhesions. The so-called Broadbent sign relates to a systolic retraction of the lower ribs in the left laterial and posterior region of the thorax. Another sign is the depression of the lower part of the sternum during the inspiratory phase.

The *treatment* of the isolated form of mediastinopericarditis is a physiologic approach consisting of resection of the ribs involved in the process. However, in most cases, cardiolysis is

sound may be accentuated due to an associated pulmonary hypertension

Circulatory Measurements

Blood pressure readings usually show a lowered systolic and reduced pulse pressure; venous pressure may be elevated. The circulation time is prolonged, both through the right and left heart, and the circulating blood volume is usually increased. The vital capacity is often reduced The findings obtained by cardiac catheterization have been discussed

Laboratory Manifestations of the Pathophysiologic Changes

The *electrocardiogram* shows abnormalities similar to those in massive pericardial effusion, namely, abnormally low voltage of QRS and T The latter may be inverted In contrast to the T wave changes in acute pericarditis, those seen in constrictive pericarditis are usually stationary The P waves are abnormal in one-half of the cases, widening and notching and atrial fibrillation are not uncommon This latter phenomenon and the P wave changes may be ascribed to myocardial injury caused by compressing scar tissue or increased intra-atrial pressure

The low voltage of QRS and T waves tends to revert to normal after cardiolysis. A failure to respond is an unfavorable sign, suggesting serious myocardial atrophy Acute cardiac failure may supervene, due to the suddenly increased inflow load

Roentgen Findings

The most significant finding in the x-rays is the presence of pericardial calcification encircling the cardiac silhouette over a variable distance. It is best observed in the oblique films. The cardiac size is usually normal or smaller than normal, the former depending on previous myocarditis or valvular lesions Pleural changes such as effusion or thickening also may be noted. *Fluoroscopy* reveals either normal or absent cardiac pulsations.

Other Laboratory Features

A low serum albumin has been noted in cases of long-standing constrictive pericarditis, as in liver disease caused by severe hepatic congestion of long duration. The acute phase reactants may be abnormal, particularly in cases of tuberculosis, notably when the active infection had been present during the constrictive phase.

Differential Diagnosis of Conditions with Similar Physiologic Disturbances

Differentiation rests mainly between myocardial disease with severe congestive failure and constrictive pericarditis. The absence of cardiac enlargement and a history of coronary artery disease with typical electrocardiographic findings usually excludes the possibility of disease Pericardial calcification, small or absent cardiac pulsations, a pulsus paradoxus, a narrow pulse pressure and the inadequate response of the congestive changes to digitalis administration support the diagnosis of constrictive pericarditis

Other conditions which may resemble constrictive pericarditis are mitral stenosis, tricuspid lesions and hepatic cirrhosis *Mitral stenosis* may be suspected in cases with peripheral congestive failure, atrial fibrillation and the absence of a palpable apex beat Also, the early diastolic adventitious sound of constrictive pericarditis may be mistaken for the opening snap of mitral stenosis A systolic retraction of the mid and upper precordium and the early diastolic rebound, however, suggest the possibility of constrictive pericarditis Fluoroscopy, cardiac catheterization and phonocardiography are helpful procedures in differential diagnosis. *Tricuspid insufficiency* can be ruled out by the characteristic configuration of the venous pulse. *Tricuspid stenosis* in certain cases may closely simulate constrictive pericarditis, the frequently associated presence of mitral stenosis facilitates the differential diagnosis. *Hepatic cirrhosis* can be ruled out by the finding of an abnormal systemic venous pressure In *primary systemic amyloidosis* gingival biopsy may be helpful diagnostically *Primary myocardial and endocardial fibrosis* sometimes responsible for the pathophysiologic changes mimicking constrictive pericarditis should be closely studied, notably in the absence of pericardial calcification.

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5 intra atrial block; intraatrial dissociation
6 atrial standstill

C. Disturbances involving the A-V node

2 atrioventricular nodal rhythm
3 *A-V nodal escape, including coronary sinus rhythm*
4 A-V nodal extrasystoles
5 nodal paroxysmal tachycardia
6 atrioventricular dissociation
7 interference dissociation
8 reciprocal rhythm

D Disturbances involving the ventricles

1 ventricular escape
2 ventricular extrasystoles
3 ventricular paroxysmal tachycardia
4 ventricular flutter and ventricular fibrillation
5 *cardiac (ventricular) arrest*
6 pulsus alternans

Physiologic Considerations

In a discussion of the causes and methods of production of cardiac arrhythmias it is pertinent to discuss first the propagation of the normal cardiac impulse and its variations within the normal range, and second, the disturbances that occur in the heart that lead to the production of the various types of cardiac arrhythmias.

Normal Mechanism

All portions of the heart muscle, including the nodes and specialized conducting tissue, possess certain fundamental properties: excitability *(irritability), rhythmicity, contractility* and conductivity. While these properties are common to the entire heart muscle, certain of them are *more highly developed in particular* parts of the myocardium. For example, excitability and rhythmicity are more highly developed in the muscle fibers that constitute the *sino-atrial node than in the rest of the cardiac* muscle.[12] For this reason this structure is the normal pacemaker of the heart

With a normal mechanism, impulses arise in the S-A node quite regularly at a rate usually between 60 and 120 per minute (Fig. 1). From the sino-atrial node the impulse spreads *radially through the atrial muscle at a rate of* approximately 1,000 mm per second and, in doing so, produces the P wave of the electrocardiogram. The impulse then enters the A-V node. This structure possesses all of the common fundamental properties of heart muscle

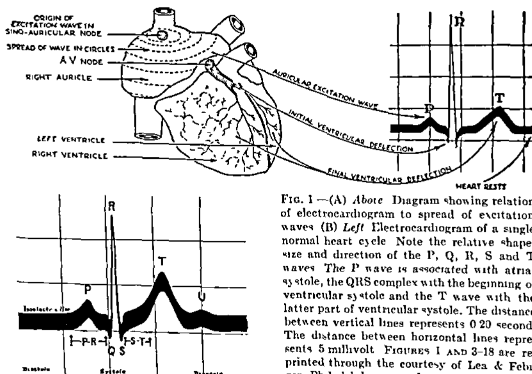


Fig. 1 —(A) *Above* Diagram showing relation of electrocardiogram to spread of excitation waves (B) *Left* Electrocardiogram of a single normal heart cycle Note the relative shape, size and direction of the P, Q, R, S and T waves The P wave is associated with atrial systole, the QRS complex with the beginning of ventricular systole and the T wave with the latter part of ventricular systole. The distance between vertical lines represents 0 20 second The distance between horizontal lines represents 5 millivolt Figures 1 and 3–18 are reprinted through the courtesy of Lea & Febiger, Philadelphia; see reference 2)

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Cardiac Arrhythmias

By SAMUEL BELLET, M.D.

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THE subject of cardiac arrhythmias is of considerable importance for several reasons: These disturbances are common, they frequently produce intense anxiety on the part of the patient, the rapid rate often precipitates heart failure The arrhythmia can in most instances be diagnosed easily, either clinically or by graphic methods, and results of treatment of these disturbances are among the most satisfactory observed in any field of medicine

The term "arrhythmia" is frequently used synonymously with clinical disorders of the heart beat and disturbances of the cardiac mechanism. The latter terms are preferable because, while the rhythm is often irregular, many of these disorders, e g , paroxysmal atrial tachycardia, atrial flutter or complete heart block, display an absolutely regular rhythm.

The following information is of help in establishing the underlying clinical etiology the age of the patient, the ventricular rate, the type of heart problem and the type of arrhythmia. These disorders are comparatively rare below the age of 10. From 10 to 20 years the types of irregularities encountered are sinus arrhythmia (usually phasic in type), extrasystoles, atrial fibrillation and varying degrees of atrioventricular heart block Between the ages of 20 and 30 most of the irregularities which are observed are those seen in rheumatic heart disease, namely varying degrees of atrioventricular heart block, atrial fibrillation and extrasystoles. From 30 to 45, syphilitic heart disease is also encountered Although atrial fibrillation is rare in *syphilitic* heart disease, various degrees of atrioventricular heart block, extrasystoles and paroxysmal tachycardia are encountered In addition, disturbances in the cardiac mechanism following digitalization are observed

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From the age of 45 on, one encounters a preponderant number of hearts of the degenerative type

Other factors of importance in the diagnosis and treatment of arrhythmias are the underlying heart condition, the presence of heart failure, the symptoms and signs presented by the patient, the response to carotid sinus pressure and, finally, the electrocardiographic findings

An ectopic rhythm should be suspected from the following: (1) the presence of any irregularity, (2) a rate below 30 or above 140 per minute with regular rhythm, (3) history of sudden onset of rapid rate, (4) rapid rate coinciding with onset of failure, (5) sudden halving of rate with carotid sinus pressure, (6) variation in intensity of first heart sound with slow or rapid rate, (7) no change in rapid rate from moment to moment following exercise and (8) electrocardiographic findings

For the sake of brevity, only some of the more common disturbances of the cardiac mechanism will be discussed

Classification of Arrhythmias

The arrhythmias may be divided into four groups, according to the portion of the heart in which they arise.[2]

A *Disturbances of rhythm involving the sino-atrial node*

1 sinus arrhythmia
2 sinus bradycardia
3 sinoatrial heart block
4 prolonged sinus pauses (cardiac standstill) and nodal escape
5 wandering pacemaker
6 sinus tachycardia

B *Disturbances involving the atria*

1 atrial extrasystoles
2 atrial paroxysmal tachycardia
3 atrial flutter
4 atrial fibrillation

causes a fall in pH. For example, at pH 7.0 complete heart block results in the experimental animal, and with lesser degrees of acidosis there is a slowing of the heart due to depression of the S-A node. Low CO_2 tension, if accompanied by alkalosis, increases the rate of conduction over the atrioventricular bundle, the rhythmicity of the S-A node is increased and the tone of the cardiac inhibitory center is lowered

It is well known that potassium, calcium and sodium are necessary for the normal beat of the heart Calcium increases contractility and prolongs systole, potassium decreases contractility and prolongs diastole; the role of sodium is not clearly demonstrable, but in perfusion experiments it is well known that solutions of calcium and potassium without sodium will not maintain the heart beat. Calcium decreases and potassium increases the permeability of the cell membrane to the hydrogen ion

Metabolic Factors in Cardiac Arrhythmias

The subject of myocardial metabolism is of considerable interest to the internist and cardiologist. *In cardiac arrhythmias the subject is* important from the following standpoints (a) What disturbances in cardiac metabolism may lead to the production of arrhythmias? These may not be specific for arrhythmias, but for cardiac disturbances in general. (b) What is the effect of arrhythmias, especially prolonged tachycardia, slow heart rates and periods of cardiac arrest, upon cardiac metabolism? Such data may be of help in therapy (c) What is the effect of various drugs and other therapeutic measures used in therapy upon the cardiac metabolism? There is a paucity of such data, and (d) what are the effects of certain procedures and states, e.g , anesthesia, hypothermia and toxic states on cardiac metabolism?

The metabolic factors involved include the effect of the arrhythmia on oxygen utilization, the requirement of carbohydrates (glucose and lactate), amino acids and fatty acids In addition, the arrhythmia *may modify* to a greater or lesser degree the factors involved in energy utilization, e g , the utilization of carbohydrates and the active transport of electrolytes and metabolites. These factors may have an effect on ATP production and utilization.

Diagnosis of Arrhythmias

Proper therapy depends on. (1) the correct diagnosis *of the type of arrhythmia*; and (2) definition of the alteration in the cardiac function underlying its production. The former may *be obtained from* the electrocardiogram, but the latter is often difficult to ascertain, even though a complete history, physical examination and laboratory data have been obtained.

Improved methods of diagnosis have resulted from. (1) *the greater* availability and use of more simplified, relatively inexpensive portable electrocardiographic apparatus, *including the new transistor models* for use in the wards of the hospital, operating room and at the patient's home; (2) the more frequent employment of continuous electrocardiographic *monitoring during surgery, cardiac catheterization and infusion of cardiac drugs in bad-risk* patients, and (3) the training of interns, residents and anesthesiologists in the diagnosis of specific arrhythmias, which has resulted in earlier and more definitive therapy

General Methods Available in Therapy

Many important advances have been made in the therapy of cardiac arrhythmias within the last decade[8] These have resulted from a combination of many factors (1) improved methods of diagnosis, (2) an increase in our knowledge of the causes, mechanism of production and precipitating factors tending to induce cardiac arrhythmias, (3) improved information relative to the more scientific use of older anti-arrhythmic drugs, e g , digitalis, quinidine and Isuprel and (4) the use of relatively new measures

Available Methods of Therapy

Some of the important advances in the treatment of cardiac arrhythmias are discussed under the methods of therapy mentioned below:

Vagal stimulation Vagal stimulation is efficacious in supraventricular tachycardias, particularly those of atrial or nodal origin This may be accomplished by mechanical means (carotid or ocular pressure), drugs or a combination of both *Carotid sinus pressure, properly applied*, is often effective in terminating the arrhythmia; *ocular pressure is not* recommended because it

but is specialized in that its refractory period is long and its ability to conduct is poor (only 200 mm per second). Most of the P-R interval through the A-V node and bundle of His Having passed these structures, the impulse enters the branches of the bundle of His and the Purkinje fibers, where its passage is rapid (4,000 mm per second)[19, 20] The impulse then enters the muscle of the ventricles, causing them to contract Once contraction is completed, the muscle returns to a resting state and remains so until another impulse is generated.

Among the important features of a normal mechanism, therefore, are (a) regularity of the formation and normal configuration of sinus impulses and the resulting P wave The P waves are upright in Leads I, II, aVF and the precordial leads (V leads), except V_1 and occasionally V_2, the P wave is normally inverted in aVR, (b) a rate that is within the normal range (between 60 and 110 per minute approximately), (c) every P wave is followed by a ventricular response; (d) every ventricular complex is preceded by and is a response to a preceding P wave, (e) the P-R interval is between 0 08 and 0 21 second in duration, (f) the impulse reaches both ventricles simultaneously and the QRS complexes are of normal duration (0 04 to 0 10 second)

Where there is a departure from features a, c, d or e, the mechanism is no longer normal Such a departure constitutes a cardiac arrhythmia or a clinical disorder of the heart beat

Role of the Nervous System

The nervous system, particularly the higher centers in the brain and in the spinal cord, often plays a role in the production of extrasystoles.[2] The higher centers include those in the cerebral cortex, the vasomotor center in the floor of the fourth ventricle, the sympathetic centers situated in the basal ganglia and the vagal centers situated in the medulla The function of these centers is affected by (a) emotional stimuli, (b) disturbances in various parts of the body, (c) carbon dioxide tension, (d) changes in pH and (e) anoxia and other chemical factors. The nerves that immediately control the heart action include the vagus, sympathetic nerves and their respective ganglia

The effects on the nervous system may be modified by certain vascular reflexes These include (a) the carotid sinus reflex, (b) reflexes from the carotid and aortic bodies, (c) aortic or depressor nerve reflexes, (d) reflexes from Pacinian corpuscles in the mesenteric vessels, (e) reflex antagonisms controlling the heart rate, (f) reflexes from the pulmonary artery and its branches, (g) Bainbridge reflex (h) Branham reflex, (i) venous reflexes and (j) reflexes from the right atrium.

Control of the Heart Rate

The rate of the heart is determined by the pacemaker Its natural tempo is controlled by a balance of antagonistic forces, e g.: (a) cardio-inhibitory forces (vagal) originating from the nucleus ambiguus in the medulla. This center can be affected reflexly or by higher centers, (b) cardioaccelerator forces arising in the upper five dorsal segments of the cord and centers in the hypothalamus and cortex Somatic impulses and vascular impulses from carotid sinus and right atrium and aortic bodies also influence the heart rate

Chemical Regulation (Role of Electrolytes)

The chemical constituents usually concerned with the regulation of cardiac function include humoral substances and certain electrolytes Loewi[202] showed conclusively that cardiac inhibition resulting from vagal stimulation is due to the liberation of acetylcholine Similarly, acceleration following stimulation of the cardiac nerves is due to the liberation of an adrenalin-like substance The heart is rich in the enzyme cholinesterase and thus vagal effects are brief

The specific products of metabolism which are known to be vasodilators include the hydrogen ion, carbon dioxide, the lactate ion, phosphate, adenosine and related compounds, and histamine Acidity, histamine and adenosine triphosphate are strong vasodilators and are probably effective even in the minute concentrations involved during mild physical activity, especially if reinforced by carbon dioxide and lactates

The junctional tissues are especially sensitive to high tensions of CO_2, A-V conduction becomes markedly depressed when the CO_2 excess

ciated with shift in plasma electrolytes and may manifest a profound effect on the production of arrhythmias. In a general way, the tendency is for alkalosis to increase and acidosis to decrease cardiac rhythmicity.[19] There are many exceptions to this, and the specific factors that are operative in a given case are not always easy to elucidate.

A shift in pH may also alter the effects of existing concentration of digitalis, quinidine, procaine amide and other drugs. For example, it has been shown recently that quinidine acts by preventing the efflux of potassium from the cells to the extracellular space and the influx of potassium from the extracellular fluid into the cells.[17] The shifts may be altered by changes in pH. The use of solutions to return acid-base balance to normal will often have a salutary effect in reducing an important cause for the production of ectopic rhythms.

Improvement in Cardiac Function

Frequently ectopic rhythms are produced by derangements in cardiac function which are associated with various types of myocardial disease and cardiac strain. These may result in the production of angina or congestive failure. The removal or decrease of this strain by rest, diuretics and various measures which are directed at the cause and which improve the underlying clinical state, will have an important indirect effect on the abolition of the ectopic rhythms.

Digitalis. Digitalis, aside from its effect in improving cardiac function, is an important antifibrillatory agent and is indicated in the control of the ventricular rate in atrial fibrillation, conversion of atrial flutter to atrial fibrillation and in the treatment of atrial and nodal tachycardias. It will often abolish extrasystoles that are associated with congestive failure.

Digitalis toxicity. Digitalis toxicity will produce almost any type of arrhythmia, including atrial and nodal tachycardias (rarely atrial flutter and fibrillation), paroxysmal tachycardia with A-V block, various degrees of A-V heart block, A-V dissociation and ventricular tachycardia. The treatment consists of (a) prophylactic measures to prevent toxicity; (b) restoration of normal acid-base and electrolyte balance to normal, (c) use of potassium; and (d) cautious use of quinidine or procaine amide, which may be effective if potassium fails.

The use of electrical devices. Recently, many devices to increase cardiac rhythmicity and to defibrillate the heart have been developed, these have proved to be invaluable in the therapy of various cardiac disorders. The following may be mentioned.

External pacemaker. The pacemaker[22] which may be applied to the intact chest has been successful in the restoration of cardiac beating. Cardiac resuscitation has occurred in patients with cardiac arrest of various etiologies. It is claimed that the artificial external pacemaker acts like a natural intracardiac parasystolic focus, except that it is under complete control. This device is now widely applied and its value in therapy established.

External defibrillator. Episodes of ventricular fibrillation occurring in the Stokes-Adams syndrome and during cardiac catheterization have been terminated by the use of an external defibrillator which applies an electric countershock across electrodes on the chest. This procedure is regarded as safe, practical and rapidly effective.[23] If defibrillation should be followed by ventricular standstill, the heart can be stimulated by the artificial cardiac pacemaker. If these measures are not immediately effective (within 30 to 90 seconds) thoracotomy and cardiac massage should be performed.

Internal pacemaker. Recently an internal pacemaker has been developed of which several models are available. We have had experience with one of these (Atronic Pacer).[f] This weighs only 2 pounds (FIG. 2) and may be used in the following manner: (1) the direct insertion through the intact chest wall by means of a needle which makes contact with the myocardium, (2) in patients with frequent Stokes-Adams attacks, the electrode has been placed by means of a catheter inserted into the external jugular vein, the proximal end of which is situated in the conus area of the right ventricle. The distal end of the electrode is attached to the pacemaker. Such pacemakers have remained in situ for as long as 8 to 10 weeks; (3) If cardiac arrest occurs during cardiac operations, or if a thoracotomy has been performed, the wire may be inserted directly into the myocardium. The advantages of such a pacemaker

carries with it the danger of retinal detachment. The use of emetics, e.g., ipecac, is another method of producing vagal stimulation. Of the parasympathetic drugs, Prostigmin, administered intramuscularly, and digitalis (oral, intramuscular or intravenous) are probably the safest

Drugs which decrease excitability The most important of the drugs which decrease excitability are quinidine, procaine amide and potassium salts. These are indicated in the treatment of extrasystoles and paroxysmal tachycardias of atrial and nodal origin, as well as those of ventricular origin

Quinidine The use of plasma levels has been a considerable aid in therapy, the therapeutic level usually ranges between 4 and 10 mg per liter However, toxic effects may occur at the higher levels The value, as well as the limitations, of plasma levels in therapy should be considered in the individual patient In patients who receive quinidine for long periods it is difficult, with the usual doses administered, to maintain an effective concentration of quinidine during the entire day Recently, a long-acting quinidine preparation (quinidine gluconate) has been developed[5] which in a dose of about 1 2 Gm per day (0 4 Gm , 3 times a day) will maintain a continuous effective level Recent experimental observations have shown that the cardiotoxic effects of quinidine, consisting of widened QRS complexes and hypotension, may be reversed by molar sodium lactate These observations have been made in the dog and in some human cases [6]

Procaine amide. Procaine amide is a very effective anti-arrhythmic agent and is indicated in extrasystoles and paroxysmal tachycardia of atrial, nodal and ventricular origins. It may be administered orally, intramuscularly or intravenously. The preferred parenteral route is by intramuscular injection, because an effective level is attained within one-half to one hour and because hypotensive effects are relatively minor Since the intravenous route is mandatory in cases of marked hypotension or shock, it is suggested that the infusion be given in conjunction with vasopressor agents (norepinephrine); the first 500 mg may be given at a rate of 100 mg. per minute Thereafter, subsequent injections should be given at a rate of 100 mg. every four minutes. Patients receiving intravenous infusion should be continually monitored electrocardiographically.

Drugs which increase excitability The drugs which increase excitability include the sympathomimetic group (epinephrine, Isuprel, ephedrine, molar sodium lactate, etc). They are indicated particularly in the treatment of slow heart rates and periods of cardiac arrest during Stokes-Adams seizures and other states

Electrolyte Alterations

One of the most significant advances in therapy has been the knowledge that the electrolyte alterations observed in disturbances of acid-base balance, involving particularly potassium and, to a lesser degree, sodium and calcium, may precipitate ectopic rhythms The restoration of normal electrolyte balance will frequently restore normal rhythm

Potassium Alterations in potassium have been studied most extensively Hypopotassemia results in the production of various types of ectopic rhythms (extrasystoles, atrial tachycardia with and without A-V block, paroxysmal atrial fibrillation and other arrhythmias). Often its presence may be obscured by the underlying clinical state, e g , congestive failure, toxic states, gastrointestinal and renal disease These arrhythmias usually respond poorly to measures other than potassium administration.[11]

The arrhythmias observed with hyperpotassemia include nodal bradycardia, extrasystoles and a slow idioventricular rhythm In addition, we have recently noted in a number of patients rapid nodal tachycardias due to hyperpotassemia (rate of 140 to 160 per minute). These can be reversed almost immediately by the use of molar sodium lactate.[8]

Other electrolytes The effects of other individual electrolytes in the production of arrhythmias have not been studied extensively. The effects of magnesium, except for a specific deficiency of this electrolyte, are generally quite similar to those of potassium The levels of serum sodium and calcium are important because they are pharmacologic antagonists of potassium; a low sodium or calcium would tend to enhance, whereas an increased sodium or calcium would decrease the potassium effect.

Alterations in acid-base balance are asso-

Symptoms and Signs

The symptoms and signs of atrial flutter are similar to those of other types of accelerated heart action except for the greater tendency to develop heart failure. Since atrial flutter is often observed in the presence of pre-existing myocardial damage in the older age group, and owing to the relatively long duration of the attacks, there is an opportunity for the occurrence of exhaustion of the heart muscle with resulting heart failure.

As a result of the rapid ventricular rate, a pulse deficit is often observed. In many cases, there is an associated pulsus alternans. With slow ventricular rates (40 to 60 per minute) one occasionally can hear the individual atrial beats. These have been recorded graphically. With one-to-one flutter, the ventricular rate ranges from 220 to 280 per minute (Fig. 3C), the heart muscle becomes rapidly exhausted and the patient presents the picture of shock, with a severe grade of both right and left heart failure. Embolic phenomena are observed in about 4 per cent of these patients.

Diagnosis

The diagnosis of atrial flutter is to be considered in any patient presenting evidence of an ectopic rhythm with a regular apical rate ranging from 140 to 180 per minute. It must be differentiated from all varieties of paroxysmal tachycardia, from rapid simple tachycardia and, when the ventricular response is irregular, from atrial fibrillation. With three-to-one and higher grades of atrioventricular heart block, it is difficult to diagnose atrial flutter except by graphic methods (Fig. 3).

Carotid sinus pressure in atrial flutter results either in no ventricular slowing or in ventricular slowing which is maintained only during the period of carotid sinus pressure, the rate returning immediately to its original speed when the pressure is removed. The effect of carotid sinus pressure in atrial flutter is enhanced by digitalis, Prostigmin and other vagal stimulants, so that carotid sinus pressure which alone was previously ineffectual may become effectual after the administration of these drugs.

The diagnosis of atrial flutter usually is clearly established by the electrocardiogram. Although any lead may be used, atrial waves are most clearly delineated in the V_1 position of the precordial leads and are best seen directly after carotid sinus pressure, as a result of which atrial cycles are unobscured by the ven-

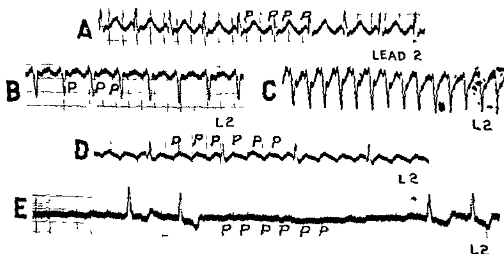


Fig. 3.—*Atrial flutter showing different types of atrial complexes and varying degrees of A-V heart block.* (A) Atrial flutter with a 2:1 heart block. The atrial rate is 250 per minute, the ventricular rate is 125 per minute. (Note that the atrial complexes are obscured by the QRS complexes and T waves.) (B) Atrial flutter with a 2:1 heart block. (Serial tracings with 2:1 and 3:1 A-V heart block more clearly show flutter waves.) (C) Atrial flutter with a 1:1 response (atrial and ventricular rate is 250 per minute). This diagnosis of the atrial mechanism was clearly established by other strips that showed higher grades of A-V heart block *(Strip B)*. (D) Atrial flutter with a 4:1 response. (E) Atrial flutter with a very high degree of A-V heart block and A-V nodal escape.

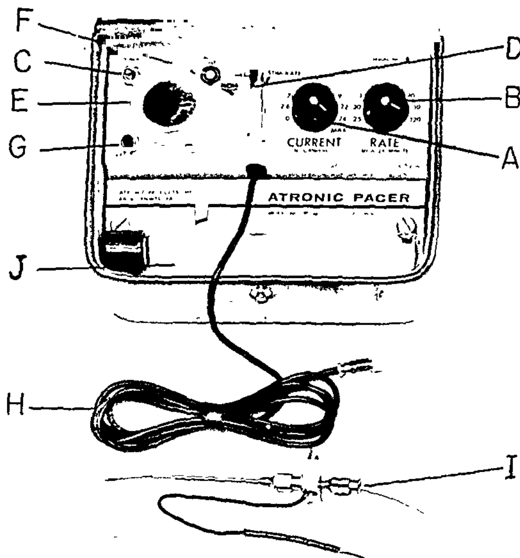


FIG 2—"Atronic Pacer/Monitor" (weight 2¼ lb) (A) Current control (B) Rate control (C) Power control (D) Function selector switch (E) Galvanometer (F) Audio jack (G) Battery test (H) Patient lead (I) Needle for insertion into heart muscle (J) Container for needles (Courtesy of A M A Arch Int Med, see reference 7)

are: (1) The voltage output required is quite small (1.5 to 4 5 volts); (2) it is accompanied by no sensations, contractions of the skeletal muscles or infection, (3) they can easily be carried about by ambulatory patients.

Monitoring devices The use of a monitoring device with a warning signal to detect the occurrence of cardiac arrest in patients with Stokes-Adams seizures, and in those prone to develop episodes of cardiac slowing or cardiac arrest during or following surgical or other procedures, is a valuable aid in treatment. Such patients should be placed in a special ward, and

of restoring the cardiac beat on notification by the warning signal The amount of time available to obtain adequate resuscitation with normal brain function is extremely short, only four minutes This time may be prolonged by the use of hypothermia

ATRIAL FLUTTER

Atrial flutter is usually seen in patients with moderately advanced or a severe grade of myocardial involvement. It is observed most frequently in association with the degenerative group of heart diseases and in patients with

Quinidine sulfate is the drug of second choice in the treatment of atrial flutter and, for all practical purposes, its use should be restricted to those cases in which digitalis has failed to break up the flutter. Quinidine is successful in converting atrial flutter to a normal sinus rhythm in about 30 to 50 per cent of cases. This drug is a protoplasmic poison and should be used with caution, especially when large doses are required and in the presence of severe myocardial damage.[2, 13] In the presence of congestive heart failure it should rarely be used. Quinidine, when successful, usually converts the flutter directly to normal sinus rhythm without an intermediate period of atrial fibrillation

The atrial rate under quinidine may drop to as low as 135 per minute The ventricular response also changes, due to vagal paralysis The degree of atrioventricular heart block changes from 2:1 to 1:1, so that with an atrial rate of 135 per minute the ventricular rate may also be 135 per minute

Results of Treatment

In summary, the conversion of atrial flutter to normal rhythm or atrial fibrillation may be accomplished by digitalis in about 60 to 80 per cent of patients. One of the causes for failure is inadequate digitalization, the careful administration of digitalis while watching the patient for possible toxic effects will result in a higher percentage of successes Quinidine results in conversion to normal rhythm in from 30 to 50 per cent of patients Here again, insufficient quinidine has been the cause for failure The spacing of dosage is extremely important in order to gain optimum therapeutic plasma levels, and favorable clinical effects

The value of procaine amide (*Pronestyl*) in the treatment of established flutter has thus far proved disappointing in most hands Conversion to normal rhythm only occasionally occurs, and this entails large doses which may be within the toxic range. The use of procaine amide in the paroxysmal form yields much better results. The final role of procaine amide in the therapy of atrial flutter has yet to be evaluated

Prognosis

The prognosis depends on the duration of the flutter, the ventricular rate, the condition of the myocardium and the response to treatment. Because atrial flutter usually occurs in patients with heart damage, often of the severe grade, the prognosis is in some instances unfavorable. Instances of atrial flutter have been known to last, *uninterrupted*, for 5 to 10 years. This duration, however, is unusual. The prognosis is poor in the presence of recurrent attacks and in those cases which require large doses of digitalis or quinidine for conversion It is unfavorable with recurrent attacks of one-to-one flutter The occurrence of paroxysmal atrial flutter in patients of the younger age group does not necessarily carry with it a bad prognosis, however, recurrent attacks in older patients and in those with heart damage is an unfavorable sign In the presence of acute myocardial infarction, the prognosis is usually poor

ATRIAL FIBRILLATION

Atrial fibrillation is probably the most important of the arrhythmias It is the one most commonly observed in the presence of congestive failure, being observed in about 60 per cent of these cases, and in this arrhythmia, digitalis is almost uniformly effective in slowing the ventricular rate

Atrial fibrillation is almost always observed in the presence of myocardial disease which is frequently of an advanced grade It is rarely seen in normal hearts The most frequently associated or causative factor is hypertensive arteriosclerotic cardiovascular disease, and the next most frequent is rheumatic heart disease These two conditions account for about 90 per cent of the cases of atrial fibrillation Other etiologies are thyrotoxicosis and toxic states It is rarely observed in syphilitic heart disease except in association with hypertension and/or arteriosclerosis In children and young adults, rheumatism is the most frequent etiologic factor; in the later decades (fifth to seventh), during which the incidence is highest, degenerative lesions predominate. Atrial fibrillation is rare below the age of 15, it is more common in men than in women, but the preponderance of

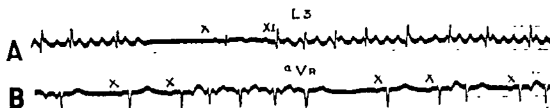


FIG 4 —Offsets and onsets of atrial flutter (impure) (A) Note the episodes of impure flutter followed by a sinus pause with restoration of normal sinus rhythm (X *and* X_1) This was promptly followed by a second episode of impure flutter (B) Similar episodes of onsets and offsets Cycles of normal sinus rhythm are marked X

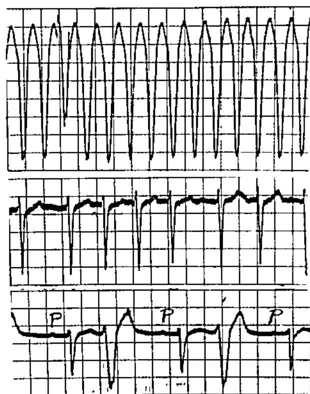


FIG 5 —Atrial flutter with a 1 1 response showing progressive changes following therapy (all leads V_1) (A) *Above* Note rapid ectopic rhythm at rate of 250 per minute This was considered to be atrial flutter with a 1:1 response (B) *Center* Following digitalis the mechanism was converted to atrial fibrillation, thus confirming the original impression of 1·1 flutter (C) *Below* Digitalis was stopped and conversion to normal sinus rhythm was spontaneous The P-R interval is top normal, 0 20 second Coupled ventricular systoles are probably due to digitalis toxicity

tricular complexes, and in esophageal leads taken at the atrial level

Treatment

Digitalis is the drug of choice in the treatment of atrial flutter. In addition to being a cardiac stimulant, digitalis will break up the atrial flutter in about 70 per cent of the cases In most instances, the flutter is converted to an atrial fibrillation * Digitalis is then stopped, after which fibrillation reverts to normal rhythm spontaneously in about two-thirds of the patients

When atrial flutter is associated with rapid ventricular rates and a severe grade of heart failure, and when absorption of digitalis may be slow or uncertain, one may resort to the use of a preparation intravenously or intramuscularly, which is somewhat safer For the intravenous route, strophanthin 0 6 mg may be used, for the intramuscular route, 3 to 5 cat units of digalen may be administered in divided doses

We have observed 2 patients in whom carotid sinus pressure following digitalization converted atrial flutter to atrial fibrillation This transition was recorded electrocardiographically

If atrial fibrillation tends to persist longer than one to two weeks following attempted conversion by digitalis, quinidine may be tried in an endeavor to convert the fibrillation to a normal rhythm The use of quinidine to restore normal rhythm is indicated in those cases of atrial fibrillation in which the onset of the irregularity is of recent origin, the heart is not severely diseased, and the enlargement of the left atrium is not considerable in degree In such instances, quinidine is successful in converting atrial fibrillation to a normal rhythm in 60 to 80 per cent of patients Occasionally, quinidine reconverts atrial fibrillation to atrial flutter.

* Occasionally flutter is converted into normal rhythm by digitalis without a recognizable period of atrial fibrillation

Treatment

Since atrial fibrillation is usually associated with varying degrees of heart failure, therapy should be directed to this state in addition to the treatment of the irregularity. Digitalis is the drug of choice in the treatment of atrial fibrillation Digitalis acts by impeding the passage of impulses from atrium to ventricle and thus slows the ventricular rate This is accomplished by a direct muscular and by a vagal effect on the atrioventricular node. The maximum therapeutic effect is said to be reached when the apical rate drops to about 70 per minute with an elimination of the pulse deficit Digitalization may be performed rapidly in patients with a severe grade of heart failure and rapid rates, or slowly in those patients in whom failure is of slight or moderate degree

The approximate dose required for a 150 pound person is about 1 4 Gm of the powdered leaf This may be given over a period of four to five days when slow digitalization is adequate, or within about two days when rapid digitalization is necessary When the patient presents a picture of severe congestive failure that necessitates rapid digitalization and definite absorption, the parenteral route is indicated Strophanthin 0 6 mg may be given intravenously, followed in two to three hours by 0 3 mg This last dose may be repeated if necessary in about five hours Digalen, 2 to 3 cat units, may be administered intramuscularly and repeated one or two times in six to eight hours, depending on the effect on the heart of previous doses Digitalis is contraindicated in patients with a slow ventricular rate (below 50 per minute), independent of treatment, and should not be given where the ventricular rate following therapy has decreased to 40 or 50 beats per minute [2] In such cases, further slowing of the ventricular rate does harm by increasing the diastolic volume, which leads to stretching of the already diseased cardiac fibers The dosage of digitalis required to produce the desired therapeutic effect varies considerably, depending upon the age of the patient and the underlying pathologic state

In the presence of thyrotoxicosis or other toxic states, and in patients with increased sympathetic tone, the dosage required to maintain a ventricular rate of 70 to 80 per minute is usually higher than the average. On the other hand, in older patients with sclerotic changes in the atrioventricular node and those with overactive vagal tone, smaller doses usually suffice to slow the ventricular rate. Patients with aortic stenosis are particularly sensitive to digitalis and usually can tolerate only small doses It should be emphasized that the reduction of the apical rate to 60 or 70 per minute does not necessarily coincide with the maximum degree of improvement insofar as signs of congestive failure are concerned Frequently edema may be present even at these slow rates In such instances digitalis should not be increased Instead, the signs of failure should be treated by diuretics and other procedures.

Toxic effects of digitalis manifest themselves by the appearance of numerous ventricular extrasystoles, coupled rhythm (FIG. 6C) and sequences of two or more ectopic ventricular beats (FIG. 7) With continuance of the drug, paroxysmal ventricular tachycardia may result This is a dangerous type of arrhythmia since it predisposes to ventricular fibrillation, which is usually incompatible with life It should be emphasized that these toxic effects may occur in the absence of nausea, vomiting and other frequently mentioned toxic manifestations These ectopic rhythms may be avoided by carefully supervising the digitalis dosage and carefully following the progress of the patient clinically and electrocardiographically. When such toxic effects appear, digitalis should be stopped immediately Should the effects continue to the stage of ventricular tachycardia, quinidine sulfate may be administered in an effort to abolish this arrhythmia

The continuance of atrial fibrillation involves three dangers The circulatory dynamics are relatively inefficient as compared with those present with normal rhythm, continuous digitalization is required and, most important, there is a constant danger of embolic phenomena leading to serious complications

Quinidine sulfate is indicated in the treatment of atrial fibrillation when it is desired to convert the irregularity to a normal sinus rhythm [18] It is indicated when the onset of fibrillation is relatively recent, when the heart

males is chiefly in the nonrheumatic group, in the rheumatic group the incidence is about equal.

Symptoms and Signs

Patients with atrial fibrillation almost invariably demonstrate evidence of myocardial abnormality, often of severe grade. They usually manifest evidence of heart failure, breathlessness, fatigue on slight exertion, precordial oppression, cyanosis, cardiac enlargement, rales at the lung bases, pleural effusion, edema of the legs and ascites.

Auscultation reveals a characteristic type of irregularity. This is most pronounced clinically at apical rates ranging from 90 to 130 per minute. When the ventricular rate is slow or very rapid, the typical irregularity is difficult to determine clinically. It is also difficult to distinguish clinically from atrial fibrillation and multiple extrasystoles arising from different foci. The irregularity due to atrial fibrillation becomes more marked after exercise Extrasystoles are usually abolished by exercise, resulting in a regular rhythm.

At fairly rapid rates during a short cardiac cycle, the ventricular contraction often fails to raise the aortic valve. As a result, one heart sound only is heard, and the ventricular contraction is too weak to produce a pulse at the wrist. When many such contractions occur, a marked variation, or pulse deficit, arises between the apical and peripheral rates.

The heart sounds vary considerably in intensity. The loudest sounds are heard following the longer pauses which permit greater ventricular filling; the faintest sounds occur following the short cycles Cardiac murmurs undergo significant changes with the onset of auricular fibrillation Systolic murmurs which were audible during normal rhythm are preserved during fibrillation They vary considerably in intensity, depending on the length of the preceding cycle, they are louder after the longer cycles and fainter after the shorter cycles, as a result of changes in ventricular filling With rapid rates, the murmurs often become inaudible The presystolic murmur of mitral stenosis, due to failure of the atria to contract, is replaced by a diastolic rumble with the onset of atrial fibrillation Its intensity and the portion of the diastole in which it is heard vary with the cycle length

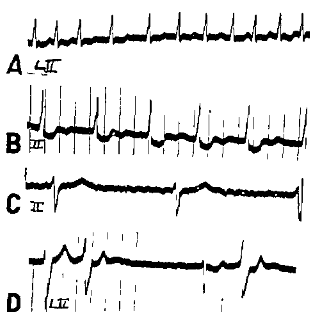


FIG 6—Atrial fibrillation with varying degrees of A-V heart block (A) Atrial fibrillation with rapid ventricular rate, 160 per minute (B) Atrial fibrillation with ventricular rate (about 84 per minute) controlled by digitalis (C) Atrial rate with probably complete A-V heart block Note the regular ventricular rate, 38 per minute (D) Atrial fibrillation with a slow ventricular rate and coupled ventricular extrasystoles, probably due to digitalis toxicity.

Diagnosis

The diagnosis of atrial fibrillation may be suspected clinically in a patient manifesting an unusual type of irregularity and who presents evidence of advanced myocardial disease of the types mentioned previously, especially if he is observed in congestive failure. The characteristic symptoms and signs have already been discussed Clinically, atrial fibrillation must be differentiated from multiple extrasystoles arising from different foci and from atrial flutter associated with varying degrees of heart block. In these two conditions, exercise tends to make the rhythm quite regular, whereas in atrial fibrillation the rhythm becomes more irregular The electrocardiogram usually establishes the diagnosis beyond doubt (FIG. 6).

as long as 10 to 15 years, few patients manage to do so.

Paroxysmal Atrial Tachycardia

Two types of paroxysmal atrial tachycardia may be observed. In the common type, the ventricles respond to every beat of the atria; in the less common type the atrial tachycardia is associated with varying degrees of atrioventricular heart block, so that with an atrial rate ranging from 150 to 200 per minute, there is a resulting ventricular rate of 75 to 100 per minute (Fig. 8). This variety is called paroxysmal atrial tachycardia with block and is most often the result of toxic digitalis effects. Patients subject to attacks of paroxysmal atrial tachycardia sometimes present electrocardiograms which, during the period of normal rhythm, show a short P-R interval with a widened QRS complex (Wolff-Parkinson-White syndrome, Fig 8) Aside from the tendency of these patients to develop this arrhythmia, their hearts may be normal

The underlying etiology in paroxysmal atrial tachycardia is not known. Since this disturbance is observed in a considerable number of hearts (about 50 per cent) which are considered clinically normal, various theories for its production have been advanced [1, 24] Among these are disturbances of the physiochemical mechanism in the atria, allergic states and high degrees of sympathetic tone In the remaining 50 per cent, this condition is observed in the presence of damage to the atrial muscle in patients with rheumatic, hypertensive or arteriosclerotic heart disease and with toxic states.

Symptoms and Signs

The symptoms of paroxysmal atrial tachycardia are similar to those observed in the presence of any ectopic rhythm and depend largely on (a) the state of the heart muscle and its response to an acceleration of the heart beat, (b) the duration of the paroxysm and (c) the nervous make-up of the patient. These may vary from a relative freedom from symptoms, except for slight palpitation, to varying degrees of precordial discomfort and a feeling of marked anxiety associated with considerable precordial pain

The signs of paroxysmal atrial tachycardia are those of an accelerated heart action superimposed on the types of hearts mentioned previously Gallop rhythm and pulsus alternans

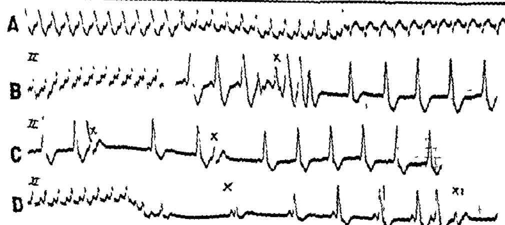


Fig 8 — (A) Atrial paroxysmal tachycardia with widened ventricular complexes (B) ... ntricular complexes resembling ... ration of normal rhythm (C) ... beats at a relatively slow rate ... atrial premature beats at X Note that these premature beats ...

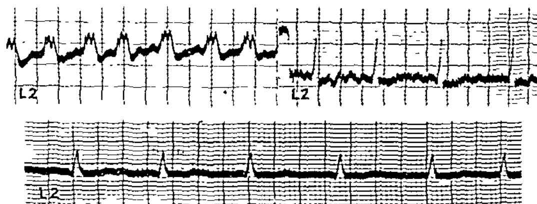


Fig 7.—(A) *Above* Widening of ventricular complexes in association with atrial fibrillation at a rapid ventricular rate. Lead II shows atrial fibrillation with widening of the QRS complexes, with a ventricular rate of 160 per minute. In the second part of A, *after digitalization* when the ventricular rate had dropped to 80 per minute, the width of the QRS complexes has returned to normal. (B) *Below* Atrial fibrillation with an almost regular ventricular rhythm. Conversion of atrial tachycardia to normal sinus rhythm. Comparison of the effect of Mecholyl (methacholine chloride) and carotid sinus pressure.

is not severely diseased and when the atria, as observed fluoroscopically are not greatly enlarged. Occasionally, restoration to a normal sinus rhythm may be indicated in the presence of moderately severe myocardial damage. In such cases, quinidine is efficient in converting the fibrillation to normal rhythm in over 50 to 70 per cent of patients.[23] Frequently, quinidine administration must be maintained for two to three months after restoration of normal rhythm, since its cessation may lead to the return of atrial fibrillation. Quinidine sulfate is also indicated in the prevention of attacks of paroxysmal atrial fibrillation, when such attacks occur frequently.

For maintenance, we have recently found that long-acting *quinidine gluconate (Quinaglute)* is superior to quinidine sulfate. A single tablet produces a prolonged effect (10 to 12 hrs.), thus avoiding multiple doses and particularly the night dose. It also prevents the valleys in plasma levels during which the arrhythmias may recur.

One of the dangers to be considered in the restoration of normal rhythm by the use of quinidine is the possibility of emboli thrown off into the circulation. Statistics relative to this occurrence vary considerably, because it is difficult to differentiate embolic phenomena which occur as a result of the underlying cardiac state. In those cases in which the fibrillation is ... duration, the danger of embolic phenomena is slight, compared with the benefits to be derived.

Atrial fibrillation which results from thyrotoxicosis usually disappears with restoration of a normal basal metabolism following successful thyroid surgery. Quinidine may be of value in those patients in whom the restoration of normal rhythm is somewhat delayed.

Atrial fibrillation which results from active rheumatic infection, toxic processes or a disturbance of metabolism tends to return to normal rhythm with the cessation of these processes unless the atrial muscle has been severely damaged, with resultant irreversible changes.

Prognosis

The prognosis in atrial fibrillation depends on the age of the patient, the underlying cardiac condition, the presence of cardiac enlargement and/or heart failure, and the ease with which the apical rate and heart failure are controlled. In general, persistent atrial fibrillation indicates the presence of a rather serious cardiac condition with impending if not actual heart failure. Some figures indicate that the mortality is 34 per cent within the first year and 75 per cent within three years. Many patients with atrial fibrillation maintain occupations involving moderate physical strain without discomfort. Although some patients may survive for

the procedure when applied as directed. The patient himself, as a result of experience, frequently employs similar procedures, such as pressure applied to various parts of the neck, particularly in the region of the carotid sinus, bending down, stretching the neck as far back as possible, holding the breath, or inserting the finger in the throat to induce vomiting The rationale of all these procedures is vagal stimulation Blowing into a balloon or a bag frequently is effective in producing sufficient vagal stimulation to stop an attack.

The following drugs may be given during the paroxysm if carotid sinus pressure fails to restore normal rhythm

1 Digitalis intramuscularly, 2 to 3 cat *units*, repeated in one to two hours if necessary Intravenous administration has also been recommended, but we rarely find this necessary Carotid sinus pressure, if previously ineffective, slows the heart beat after digitalis administration

2 *Prostigmin methylsulfate, 1 to 2 cc of 1:2000* solution, given intramuscularly While it may not be effective in itself, it increases the sensitivity of the carotid sinus about twenty minutes after its administration, so that the previously insensitive carotid sinus is frequently rendered sensitive to stimulation

3 Procaine amide (Pronestyl) will stop the attack in about 80 per cent of the cases[18] The parenteral route, preferably intramuscular, is the one choice The dose is 500 mg, which may be repeated 2 to 3 times at intervals of two to three hours

4 Magnesium sulfate, 10 cc of a 20 per cent solution administered intravenously

5 Calcium gluconate, 10 cc of a 10 per cent solution administered intravenously If the drug is efficacious, the paroxysm will cease immediately This should never be used concomitantly with digitalis

6 Quinidine sulfate, 0 3 Gm administered intramuscularly at hourly intervals for 5 or 6 doses or more Quinine dihydrochloride, 0 3 Gm dissolved in 20 to 50 cc of normal saline solution, may be given slowly by vein or an ampule of 5 cc may be given subcutaneously Quinidine may be given by mouth, 0 2 or 0 3 Gm every hour for 10 or more doses

7 Mecholyl, 25 to 50 mg subcutaneously This often results in cessation of the paroxysm, however, this drug usually produces a profound fall in the systemic blood pressure We have observed periods of ventricular fibrillation after its administration and advise caution in its use in the very young or the very old, and in asthmatic individuals When the drug is given, one should always have a *syringe of 1 3 mg* of atropine ready for administration in the event of untoward effects

8. *Ipecac given by mouth in syrup form in a dose of 1 to 4 drams to induce vomiting*

The *treatment between attacks* involves ascertaining the precipitating cause of the attacks, if possible, and treating it. Nervous states, abdominal distention, excessive exertion and allergic factors all may be provocative causes. If the paroxysms occur frequently, the following procedures are usually helpful. quinidine sulfate, 0 2 Gm given four to five times per day; digitalization, followed by a maintenance dose which may be continued for months Occasional cases are encountered in which these procedures do not suffice and the paroxysms continue In refractory cases the use of antithyroid drugs, e g., Tapazole or propylthiouracil, has been valuable in stopping paroxysms In extreme cases radioactive iodine (I^{131}) has been used with satisfactory results

Prognosis

The prognosis of paroxysmal atrial tachycardia is usually good insofar as individual attacks are concerned The prognosis is less favorable in (a) a long-continued paroxysm, (b) when severe myocardial damage is present; (c) in those infrequent instances in which the attacks recur repeatedly in spite of therapy. The outlook is unfavorable when the attacks are accompanied by precordial pain and/or cardiac collapse and in association with acute or chronic myocardial infarction

Atrioventricular Heart Block

Atrioventricular heart block may be divided into two types partial and complete The first stage of atrioventricular heart block is said to occur when the atrioventricular conduction (P-R interval) exceeds 0 20 second (Fig 9). As the degree of block increases, the conduction time becomes longer and longer until dropped beats occur, that is, the ventricles fail to respond to some atrial beats (Fig 9B). As this condition progresses, the degree of block may increase to two-to-one, three-to-one, four-to-one or still higher degrees of atrioventricular heart block. As the block further increases, a stage is reached at which the ventricles fail to respond to any atrial impulses, with the result

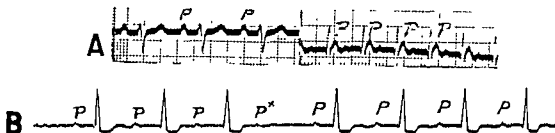


FIG 9 —Partial A-V heart block (A) Initial strip shows prolongation of the P-R interval, which measures 0 22 second. Second strip Note the P-R interval prolongation with the tachycardia (ventricular rate, 150 per minute) Note the P wave of the prolonged P-R interval is situated immediately following the preceding QRS complex and is situated between the QRS and T wave. This P wave controls the following QRS complex (B) Shows progressive increase in the prolongation of P-R interval until a dropped beat is observed at Px (Wenckebach phenomenon)

are encountered not infrequently during the paroxysm. Heart failure and the anginal syndrome may also be observed Occasionally, especially in the older age group with arteriosclerosis, the paroxysm may simulate the phenomenon of shock, resembling an acute myocardial infarction Death in paroxysmal atrial tachycardia is rare, it has been observed

Diagnosis

The diagnosis of paroxysmal atrial tachycardia should be suspected in a patient who gives a history of sudden acceleration of the heart beat which lasts for varying periods of time and stops suddenly. The previous presence of atrial extrasystoles is suggestive evidence The presence of a regular rhythm during the paroxysm, the rate of which ranges from 140 to 220 per minute, should lead one to suspect paroxysmal atrial tachycardia as the cause The differential diagnosis involves sinus tachycardia, atrial flutter and ventricular tachycardia. Of these three abnormal mechanisms, paroxysmal atrial tachycardia is the only one which, when responding to carotid sinus pressure, results in a sudden halving of the rate with restoration of the normal mechanism, the latter being maintained for relatively long periods of time. Ventricular tachycardia is uninfluenced by carotid sinus pressure, as previously stated, atrial flutter, when it responds, presents a slowing of the ventricular rate which is maintained only during the period of carotid sinus pressure * The final diagnosis is usually clearly established by the electrocardiogram.

Treatment

The treatment of simple paroxysmal tachycardia may be divided into (a) treatment during attacks and (b) treatment between attacks

The following procedure may be tried *during the attacks* application of carotid sinus pressure. In order to apply this pressure properly, the patient should be placed in the recumbent or semirecumbent position. The carotid artery should be palpated as high up in the neck as possible and pressed firmly against the vertebral column This vessel is frequently an elusive structure, and one must make certain that the carotid artery and no soft tissue of the neck is pressed *During the maintenance of pressure, a stethoscope should be applied to the precordium, and, as soon as the heart stops, the pressure should be removed* † Bilateral carotid sinus pressure should never be applied simultaneously We have never seen any accidents result from

* Occasionally, patients with sinus tachycardia, with a sensitive carotid sinus mechanism (the sensitivity possibly enhanced by digitalis) respond similarly by a sudden decrease in the ventricular rate Usually, the rate returns to the previous figure on removal of carotid sinus pressure

† Askey (Am. Heart J , February, 1946) collected 10 cases in which carotid sinus pressure resulted in either transient or permanent hemiplegia. With the technic described, we have never observed such a complication in many thousands of cases

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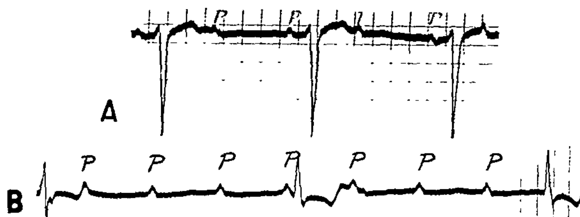


FIG. 10 —(A) Partial A V heart block (2.1) with an atrial rate of 74 and a ventricular rate of 37 per minute (B) Complete A-V heart block, atrial rate regular at 79 per minute and the ventricular rate regular at 22 per minute Note that the atria are beating entirely independently of the ventricles

that these two chambers beat entirely independently of each other When this stage is reached, the atrioventricular heart block is said to be complete (FIG 11)

Symptoms and Signs

In partial atrioventricular heart block, no symptoms are observed as being due to the block itself Even with a slow ventricular rate, the symptoms are those of the underlying disease In the usual case of complete atrioventricular heart block, the only symptoms observed are fatigue on exertion, consciousness of the slow beating of the heart and occasional precordial pain These patients usually cannot engage in strenuous physical exertion but generally do fairly well on a regimen of reduced activity

As a result of slow rate, alterations appear in the cardiovascular dynamics. The cardiac output per beat is increased, but the cardiac output per minute is decreased The systolic blood pressure rises to about 170 to 200 mm and left ventricular hypertrophy results [18] These patients are subject to Stokes-Adams attacks, which are discussed later.

Diagnosis

When prolongation of the conduction time (prolonged P-R interval) is present, a diminished intensity in the first heart sound results, which may be marked If the P-R interval is sufficiently prolonged, it may produce a gallop sound (summation gallop) This is best heard at rates over 100 per minute and is the result of atrial contraction superimposed on the wave of early diastolic ventricular filling With higher grades of partial block, dropped beats may be detected. These pauses may be abolished by exercise, they are at times difficult to differentiate from the compensatory pause following an extrasystole. Occasionally, the atrial sounds may be audible in the higher grades of atrioventricular heart block.

When the heart beats regularly between 30 to 50 per minute, an atrioventricular heart block may be suspected In partial block, exercise or amyl nitrite may abruptly double the ventricular rate. When the apical rate is regular (ranges from 20 to 40 per minute), and is unaffected by exercise or atropine, complete atrioventricular block should be suspected The first heart sound varies in intensity because of the varying atrioventricular intervals. When the atrial and ventricular contractions occur close together, the first sound is relatively loud; when they are far apart, the first sound is less intense

The important symptoms to be considered in the higher grades of partial and complete block are the development of giddiness, fainting and temporary loss of consciousness (Stokes-Adams syndrome) These seizures occur during the transition from partial to complete block, as well as during the course of complete atrioventricular heart block. They result from the periods of asystole, which last from three to nine seconds or longer, and consist of syncopal

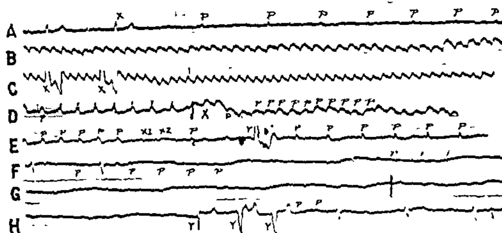


FIG 11 —Cardiac mechanisms observed during Stokes-Adams seizures All of these strips are taken from the same patient, 29 years of age, who experienced many episodes before death. Necropsy revealed diffuse lipoid infiltrations involving the A-V node. (A) Shows a cycle of complete A-V heart block with beginning of ventricular standstill (X) The atrial cycles occur at a relatively slow rate which gradually increases. (B) Shows the presence of atrial flutter, rate 240 per minute, which was maintained for periods of 20 to 30 seconds (C) Note the occurrence of idioventricular beats at X, with speeding of the rate of the atrial flutter to 310 per minute. (D) Shows an atrial tachycardia (150 per minute) during the period of ventricular standstill This changes to atrial flutter at X (E) Shows variation in the atrial rate during periods of ventricular standstill The atrial rate is initially 120 per minute Bizarre P waves are observed at X_1, X_2 and X_3 An idioventricular beat is observed at Y, following which the

ventricular beats at Y in *Strip H*

attacks or actual convulsive seizures[4] The following are the underlying mechanisms recorded electrocardiographically during the seizures (FIG 11). (a) a prefibrillary type of ventricular tachycardia, (b) ventricular fibrillation, (c) standstill of the whole heart, (d) ventricular standstill with maintenance of atrial beating. These mechanisms may occur singly or in combination Recognition of these various types is important in therapy Death frequently occurs during a paroxysm; indeed, this is the most frequent cause of death in complete atrioventricular heart block. The patient may experience many seizures, sometimes over a period of several years, before death finally supervenes

Treatment

No treatment is required for minor grades of atrioventricular heart block The treatment is that of the underlying cause if ascertained, e g, rheumatic heart disease or other *infections*. Although digitalis may be administered to patients with atrioventricular heart block, one should be somewhat more cautious in its administration because of the greater susceptibility to higher grades of atrioventricular heart block.

The higher grades of atrioventricular heart block are usually chronic and fixed The routine of the patient should be governed by his general fitness. All those who experience syncopal attacks should be warned of the danger of going about alone. We have seen such patients who have been treated for years for epilepsy Ephedrine sulfate, 24 mg. orally three times daily, or Isuprel, 10 mg sublingually, may be given to prevent such attacks.

The treatment of attacks of Stokes-Adams syndrome depends on the underlying mechanism, which unfortunately cannot be determined during the attacks except by graphic means. The following measures may be used during the attacks:

a. Direct, vigorous thumping on the precordium is particularly helpful in the presence of cardiac arrest or ventricular asystole

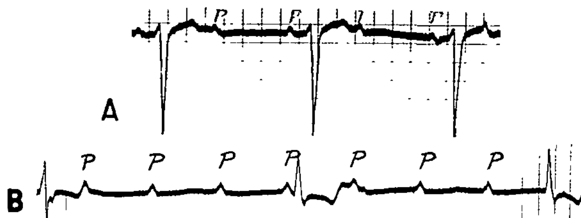


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Diagnosis

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average duration of life after the first syncopal attack was 6.9 years (the range being several hours *to eleven years*). *In many* instances syncope preceded complete heart block by a few months to a few years.

Carotid Sinus Syncope

The occurrence of transient syncopal attacks due to cessation of cardiac beating can be due to many factors. The type wherein overactive vagal tone is the important factor is not uncommon. This type of syncope may result from reflexes arising in various portions of the body which have vagal endings. There are three kinds *of* vagal reflexes which are *mediated through* the carotid sinus mechanism: (a) the cardioinhibitory form, (b) vasodepressor and (c) cerebral. The last two are rare. The first is relatively common. In the cardioinhibitory type, the syncope is the result of ventricular asystole (Fig. 12). Hypersensitivity of the carotid sinus mechanism may result from local factors as well as from disease or disturbance of any viscera supplied by the vagus. Thus, it may result from myocardial disease, coronary insufficiency, biliary tract disease, gastrointestinal disturbances, renal *colic, etc*.

The cardioinhibitory type is the most common one leading to syncope by reflex vagal stimulation. About 10 per cent of normal individuals manifest hypersensitivity of the carotid sinus, this susceptibility increases with age. This sensitivity in some instances may be produced or increased by atherosclerosis of the carotid artery, inflammatory disease around the neck, hypoxic states and certain types of myocardial damage. Certain pathologic states are associated with increased carotid sinus sensitivity, e.g., aortic stenosis, coronary artery disease and disease of the A-V node. Parasympathetic drugs, Prostigmin, acetyl beta-methylcholine and digitalis increase the sensitivity of the carotid sinus mechanism. This type of syncope probably occurs more often than one is led to believe from the literature and may be a cause of sudden death.

Treatment

This type of syncope is treated first by ascertaining the cause and removing it, if possible. The cause may be a tight collar, diverticulum of the esophagus or pathology in other portions of the gastrointestinal tract or other viscera supplied by the vagus; digitalis may be a factor. Considerable help is derived from the use of sympathomimetic drugs (which tend to neutralize parasympathetic effects), e.g., ephedrine sulfate (25 mg., 3 to 4 times a day), benzedrine (5 mg., 3 times a day) or paredrine (60 mg., 3 times a day). Injections of novocaine around the carotid sinus, either unilaterally or bilaterally, are only of temporary efficacy. Denervation of the carotid sinus unilaterally or bilaterally is of help, but in our experience *the sensitivity frequently returns* in *a number* of months. Recently, x-ray treatment directed to the area of the carotid sinus has proved successful in decreasing carotid sinus sensitivity in about 60 per cent of patients.[14]

The vasodepressor type of syncope is characterized by fainting in the erect position and is usually the result of hearing bad news, the sight of blood, severe pain, fear, poor environment, etc. It is due to a vasodilatation of the vessels in the lower part of the body and requires no special therapy. Occasionally, the depressor type occurs in association with a cardio-inhibitory type of syncope.

The cerebral form of carotid sinus syncope, originally defined by Weiss and Ferris,[27] has undergone considerable modification in recent years as a result of further study.[28] This type of syncope is due, in many instances, to cerebral vascular insufficiency. It has been *found*, by the use of arteriography, that the carotid artery opposite to the sensitive one was either occluded or severely stenosed. If one carotid artery is diseased, digital compression of the other carotid, as is done in testing for carotid sinus sensitivity, *can produce a clinical* response identical to that described in the cerebral form of carotid sinus hypersensitivity in the past. An important point in differential diagnosis of disease *of the carotid artery* is that the objective findings persist and are unaffected by the use of atropine or infiltration of the carotid sinus with procaine. This indicates that the vagal reflexes have no definite role in the production of this particular phenomenon. No cerebral response is obtained in these cases

b Epinephrine, during cardiac arrest, may be administered by intracardiac injection (0 25 to 1 ml of a 1:1000 solution). To maintain an adequate heart rate (30 to 40 beats per minute) and to prevent further seizures, particularly in a state of hypotension or shock, 0 2 to 0 3 ml of a 1:1000 solution (diluted tenfold) of epinephrine may be given by slow drip, intravenously, under careful observation

c Isuprel may be given by the following methods sublingually in doses of 10 to 20 mg every two hours, or as required, subcutaneously, 0 2 mg every six hours, or as indicated, or intravenously as a continuous infusion of 1 mg Isuprel in 200 ml of 5 per cent glucose in distilled water, or 4 μg /cm [3], at a rate of 9 to 200 drops per minute

d Molar sodium lactate, in our experience, is an extremely valuable adjunct in the treatment of Stokes-Adams seizures, especially those associated with cardiac arrest [7]

Molar sodium lactate is most effective when given promptly, preferably within one or two minutes after the onset of the attack The dose and rapidity of the administration vary considerably, depending on the type of attack and the period in which the patient is seen If the patient is *in extremis* following a relatively long period of cardiac standstill, 40 to 80 ml may be given rapidly by vein in order that some of the infusions may reach the heart In other milder episodes of relatively short duration, when the need is not so urgent, smaller doses (10 to 20 ml) may be given at one time After this, the solution should be administered as an intravenous infusion at the rate and amount depending on the effects observed As the ventricular rate increases, the infusion should be slowed down.

e Artificial pacemaker Cardiac arrest in animals has been successfully treated by the use of an electric pacemaker [7, 29]

f Defibrillation Episodes of ventricular fibrillation occurring in the Stokes-Adams syndrome have been terminated by the use of an external defibrillator which applies an electric countershock across the electrodes on the chest [30]

Prognosis

Death may occur in any attack, indeed, this is the most common cause of death in subjects with complete A-V heart block. The prognosis is best in those cases in which the complete A-V heart block is abolished and normal sinus rhythm is restored The prognosis is poor in patients with repeated episodes Penton et al in 1956,[23] observed syncopal attacks in 137 out of 251 cases of complete A-V heart block The

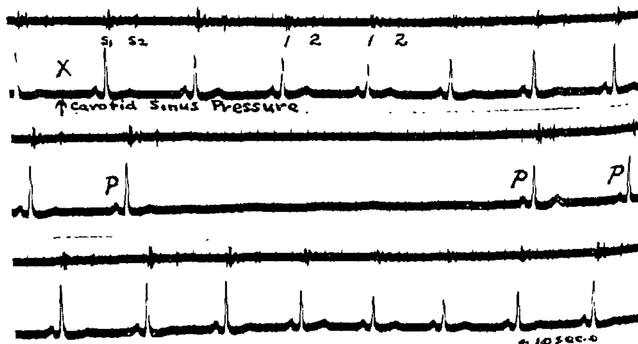


Fig 12 —Cardioinhibitory type of carotid sinus syncope (A B and C) Continuous tracing of Lead I taken simultaneously *with the heart sounds at the apex* *Carotid* sinus pressure was applied at *X* of *Strip A (above)* Note the cessation of the heart sounds and electrical activity for five seconds in *Strip B (center)* and the resumption of cardiac beating at the end of *Strip B* and slight speeding of the rate in *Strip C (below)* Note that there is no change in the character of the first heart sound following the long period of asystole in *Strip B*



Fig 13 —A-V nodal rhythm, reciprocal beat, A-V dissociation and interference dissociation (Lead II). (A) Note the presence of lower A-V nodal rhythm in the initial six cycles There is a gradual increase in the P-R interval until in cycle X the P-R interval has increased to 0 32 second, and is followed by a premature QRS complex (X) (reciprocal beat) The remaining atrial beats in this strip are upright, indicating a sinus origin and are slower than the ventricular cycles, the ventricular rate is 84 per minute, the atrial rate is 78 per minute. This represents a period of A-V dissociation (B) Shows resumption of a regular lower A-V nodal rhythm with an inverted P wave following the QRS complex (C) A-V dissociation At X the P wave captures the ventricle (A-V dissociation with interference) This sequence is repeated at X_1. (D) A-V dissociation Ventricular capture (interference beats) occur at X and X_1.

the diagnosis is sometimes uncertain and must be arrived at largely through elimination.

Transition from sinus to atrioventricular nodal rhythm and back again to sinus rhythm is not infrequent This transition may be noted by a gradual change in the configuration of the P wave from upright to inverted with a shortening of the P-R interval. This shift in the origin of the impulse has been called the "wandering pacemaker" (Fig 14)

Diagnosis

Although atrioventricular nodal rhythm may be suspected when the apical rate is regular and ranges from 40 to 50 beats per minute, the diagnosis is confirmed chiefly by means of the electrocardiogram as described above. The conditions to be differentiated are: atrial fibrillation with an almost regular ventricular response, atrioventricular dissociation, excessive sinus slowing and atrial standstill.

Prognosis

The prognosis in atrioventricular nodal rhythm depends on the underlying cardiac state The presence of this arrhythmia is but one of the considerations determining the prognosis. Persistent nodal rhythm is usually a sign of widespread myocardial damage, however

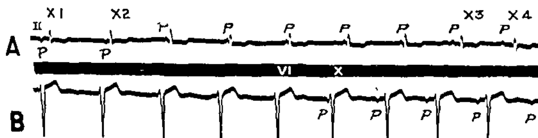


Fig 14 —Wandering pacemaker from the A-V to the S-A node in the presence of A-V dissociation (A) Note the inverted P waves at X_1 and X_2 arising from an A-V nodal site changing to upright P waves in the remaining cycles The P-R interval is within normal range in X_3 and top normal in X_4. The atrial rate is 60 per minute and the ventricular rate is 66 per minute (B) V_1 shows similar changes Note the absent P waves in the initial four cycles, probably the result of a mid-nodal origin and note the presence of A-V dissociation starting at X as the ventricular rate speeds.

when the carotid sinus compression is insufficient to impair carotid blood flow The recognition of this type of syncope is important since surgical intervention may be a curative of the syndrome

A-V Nodal Rhythm

The term "atrioventricular nodal rhythm" is usually applied when the impulses arising in the atrioventricular node, either slowly or rapidly, spread both downward to the ventricles and upward to the atria and thus control both chambers This is not always the case, however, for frequently the nodal impulses *go only* to the ventricles, the atria remaining under control of the sino-atrial node When this is the case, some other name (A-V dissociation, A-V dissociation with *interference*) is given to the disturbance (Fig 13).

Etiology

Among the causes of nodal rhythm are those conditions tending to inhibit temporarily the function of the sino-atrial node or to damage permanently that structure Vagal stimulation, certain phases of respiration and the initial stage of atropine effect may produce transient periods of nodal rhythm. Injury to the sino-atrial node by toxic processes, myocarditis, especially rheumatic carditis and degenerative states may result in relatively long periods of nodal rhythm Digitalis and certain toxic states occasionally produce nodal rhythm. When produced by such toxic factors, the ventricular rate may be 60 or more beats per minute

Symptoms and Signs

No symptoms are produced by atrioventricular nodal rhythm itself. The symptoms are those of the underlying cardiac state Shortness of breath, consciousness of the heart beating slowly, or irregular heart action are the chief complaints. No signs are observed except a persistent slow pulse usually accompanied by some degree of irregularity The rate undergoes variations, particularly following exercise or emotion, at which time the atria and the ventricles beat at a slightly different rhythm This also gives rise to variation in the intensity of the first heart sound due to the mechanism described under complete atrioventricular heart block. Occasionally, nodal premature contractions or nodal tachycardia may be associated with this disorder.

Electrocardiogram

The electrocardiographic findings differ, depending on whether the impulses arise in the head or atrial end, in the tail or ventricular end, or in the center of the node What usually is seen is a migration of the center of impulse formation with some impulses arising from one situation in the node and some from another. Regardless of which center is active, there is one common feature· The atrial P waves are inverted or at least different in shape from the P waves originating in the sinus node. This is so because an impulse arising in the atrioventricular node follows a course through the atrial muscle entirely different from the course of an impulse arising in the sinus node The QRS complexes are usually supraventricular; that is to say, of normal width and shape, though occasionally one sees a slight aberration in their shape

When an impulse arises in the ventricular end of the node, it has a much shorter distance to go to reach the ventricle than the atria. As a consequence, the ventricles are activated and contract before the atria, with the result that the inverted P waves are usually situated between the QRS complex and the T wave.

When an impulse arises in the atrial end of the node, the distance to be traversed to reach the atria is short However, as the impulse spreads from its point of origin upward toward the atria, and the P wave begins to be recorded, the impulse will also then be well on its way through the node toward the ventricles This naturally results in the P-R intervals being quite short, often 0 12 seconds or less With slow nodal rhythm (40 to 50 per minute), this variety with short P-R intervals can be recognized unmistakably Thus, the electrocardiogram becomes a significant criterion in diagnosis.

When the impulse arises at about the center of the node, it may reach the atria and ventricles simultaneously, with the result that the QRS and P waves occur simultaneously and the latter are invisible. When this is the case,

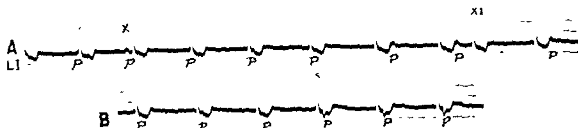


FIG 15 —A-V dissociation with interference (A and B) Continuous Lead I. The atrial rhythm is regular at a rate of 46 per minute and the ventricles beat at a rate of 48 per minute. At X a normal sinus beat is seen (Note that there is no disturbance in the ventricular rhythm at this point). At X_1 an interference beat (ventricular capture) occurs Note the shortened RR interval at the interference beat, this is not seen at the normal sinus beat at X Following the interference beat there is a longer PP interval This is followed by lower nodal rhythm seen on Strip B, shown at X

retrograde block which is responsible for the A-V dissociation

Since the atria in A-V dissociation beat at a different rate than that of the ventricles, it is almost inevitable that all instances of A-V dissociation will sooner or later develop one or more interference beats, and consequently the term "interference dissociation" is loosely applied to all tracings showing A-V dissociation Such usage only makes for confusion and varied interpretation of a given tracing.

The most common causes of A-V and interference dissociation are digitalis and occasionally quinidine toxicity, rheumatic myocarditis and coronary heart disease

EXTRASYSTOLES

Extrasystoles, or premature contractions, may arise in the sinus node, the atria, the ventricles, the A-V nodal tissue or in the His bundle They may occur rarely or rather frequently in a period of a minute. They may appear in pairs, in sequences of three or more or they may occur in the form of coupling, i e., an extrasystole following a normal beat In each instance, extrasystoles can be potential causes for the production of atrial, nodal or ventricular tachycardia.

The exact cause of extrasystoles is not known They are believed to be produced in a focus of increased or decreased irritability of the heart muscle. In some instances, they are apparently the result of functional factors and may be observed in perfectly normal hearts; in others, they are clearly the result of disease of the heart muscle, as related to various etiologies, e.g., inflammatory, degenerative, toxic states, anoxia, electrolyte disturbances and drugs, particularly digitalis

Symptoms and Signs

There may be no symptoms in the presence of extrasystoles Frequently, the patient is conscious of what he calls "palpitation" or "the heart turns over" or "the heart stops." Although extrasystoles per se may be of little or no importance, the thought that there is something wrong with the heart renders the patient panicky and he feels the imminence of a serious eventuality Occurring frequently, these symptoms may arouse intense anxiety on the part of the patient. The history frequently given is that the symptoms are more apparent while resting, particularly while lying in bed.

Diagnosis

The interruption of a normal rhythm by premature beats followed by a pause which usually, but not invariably, is compensatory is a characteristic finding on auscultation These pauses are often difficult to differentiate from those that appear during the Wenckebach phenomenon of partial atrioventricular heart block When the period between the extrasystoles and the preceding normal beat is short, ventricular filling is small and the extrasystolic beat may not be sufficiently strong to open the aortic valve and will not produce a palpable pulse at the wrist. This results in a pulse deficit.

The presence of a normal beat followed by an extrasystole repeated in regular sequence is

it may occasionally be the result of a small isolated lesion.

Treatment

There is no specific treatment for this condition, therapy should be directed toward the underlying clinical state.

A-V Nodal Extrasystoles and Nodal Paroxysmal Tachycardia

An A-V nodal extrasystole consists of a premature beat arising in the atrioventricular node. The electrocardiographic features depend on the site of the ectopic focus in the A-V node inverted P waves are situated either before, behind or buried in the QRS complexes (Fig 14) If situated before the QRS complexes, the P-R interval will be shortened If, instead of a single isolated nodal extrasystole, there occurs a series of these beats, it constitutes nodal paroxysmal tachycardia. As the name implies, it is paroxysmal and the rate may rise as high as 140 to 160 per minute This disturbance is the typical example of the rapid type of nodal rhythm, but is relatively uncommon The therapy of nodal tachycardia is quite similar to that of atrial paroxysmal tachycardia.

A-V Dissociation

Atrioventricular dissociation is that condition wherein the atria beat regularly in response to the pacemaker in the sino-atrial node and the ventricles beat regularly, at a more rapid rate, in response to the pacemaker in the atrioventricular node. Forward conduction is preserved, but there is a block of retrograde conduction through the A-V node The faster ventricular rate does not "take over" the S-A node because of the unidirectional block (retrograde) present in the A-V junctional tissue. Rarely, in A-V dissociation the ventricular rate is slower than the atrial rate This will occur when the A-V node is discharging at a faster rate than the sinus node However, there is antegrade block in the A-V junctional tissue below the site of the A-V nodal pacemaker so that many of these impulses do not give rise to a ventricular response. Thus, the ventricular rate is slower than the sinus nodal rate, even though A-V dissociation is present. In this instance, it is difficult to differentiate this mechanism from that of a minor grade of A-V heart block.

The electrocardiogram is characterized by QRS complexes of normal width (since the stimulus arises from the A-V node) which occur independently of the normal beats (Fig 14) The P waves are upright and follow successive nodal complexes at variable intervals. At times, the P waves will deform the QRS complex or be buried within it With this condition one may find that initial phases of the impulse, which are controlled by the two separate pacemakers, may meet and prevent passage into the regions that have already been stimulated Such beats are called *fusion beats* and may be labeled atrial or ventricular, depending on their origin.

Interference Dissociation

Simply stated, interference dissociation is nothing more than A-V dissociation in which an occasional sinus impulse is conducted to the ventricle (an interference beat) An interference beat occurs when an atrial impulse or a series of atrial impulses find the A-V junctional tissue nonrefractory, and therefore are conducted through the A-V node to activate the ventricles In studying an electrocardiogram demonstrating A-V dissociation with interference, the interference beats are readily recognized by the following characteristics first, the P-R interval is usually within normal range (0.12 to 0 20 second), second, the R-R interval between the preceding QRS and that of the interference beat will be shorter than the R-R intervals observed before or after the interference beat; and finally a postextrasystolic pause usually follows the interference beat (Fig 15) Rarely, an interference beat will not demonstrate the second and third criteria This can occur only when the interference beat happens to fall exactly when a ventricular beat would have been expected, thus, the R-R interval would not be shortened and no postextrasystolic pause would be seen Interference beats are distinguished from reciprocal beats by the presence of a normal upright sinus P wave between the coupled QRS complexes in the A-V dissociation Both accompany nodal A-V rhythm, but reciprocal beats occur only if there is not a complete

systoles. Gastrointestinal disturbances, foci of infection and exogenous poisons should be sought for and removed, if possible. Frequently, the cause cannot be found, and patients with the symptomatic variety of extrasystoles should be reassured that this is a normal phenomenon occurring frequently in normal hearts. If they prove troublesome to the patient, the following therapy is suggested: *quinidine sulfate*, 0.2 Gm., four or five times daily; the long-acting preparation Quinaglute, 2 to 3 tablets of 0.3 Gm per day; procaine amide, 250 mg., three times daily; or sedatives, e.g., phenobarbital, 33 mg. three times daily. Psychotherapy is indicated in those cases in which emotional problems may be a factor in the production of the extrasystoles.

Paroxysmal Ventricular Tachycardia

Paroxysmal ventricular tachycardia is a rather rare, but serious, type of arrhythmia. When a series of six or more ventricular extrasystoles occurs in succession, it may be said to constitute a paroxysm of ventricular tachycardia. Its evolution may be observed in serial tracings. Occasional ventricular extrasystoles initially present become more numerous, and later either coupled rhythm appears, or these extrasystoles occur in sequences of two or three beats. Following this, short and then long paroxysms of ventricular tachycardia may appear. A paroxysm may last a few hours, days or weeks. The danger of this disturbance lies not only in its association with a severely damaged heart and the tendency to exhaustion of the heart muscle, but also in the predisposal of the rhythm to develop into ventricular fibrillation.

Paroxysmal ventricular tachycardia almost always occurs in the presence of severe myocardial damage. It is only occasionally observed in patients whose hearts are apparently normal clinically. The following are the most important associations: toxic digitalis effects, myocardial infarction, severe grade of hypertension and arteriosclerotic heart disease.

Symptoms and Signs

The symptoms of paroxysmal ventricular tachycardia are similar to those of any ectopic rhythm but are apt to be more severe since they are observed in seriously damaged hearts.

Diagnosis

The diagnosis of ventricular tachycardia is difficult to establish clinically; it can be made definite only by the electrocardiogram. The arrhythmia should be suspected whenever the ventricular rate varies from 130 to 180 per minute and does not yield to carotid sinus pressure. Strong and Levine[25] have mentioned two factors of importance: (1) slight irregularity of the ventricular rate and (2) variation of intensity of the heart sounds because of the superimposition of atrial and ventricular contractions at various beats. The electrocardiographic diagnosis of ventricular tachycardia may be established from the following: The beats of the paroxysms must be ectopic in origin and must conform to those observed as isolated extrasystoles before the onset of the paroxysms; the first beat of the paroxysm must bear the same relation to the preceding normal beat as a coupled extrasystole bears to the preceding normal beat; the ventricles must be observed to beat regularly at a rate of 130 to 180 per minute (Fig. 17A); and the atria must also beat regularly, slower than and entirely independent of the ventricles (Fig. 17B). Occasionally, ventricular tachycardia is observed in the presence of atrial fibrillation. Less commonly, ventricular tachycardia may give rise to retrograde P waves (Fig. 18A).

The differential diagnosis from the electrocardiographic standpoint involves any ectopic rhythm in which the QRS complexes are widened as a result of fatigue of one of the bundle branches incident to the rapid rate. Such widening of the QRS complexes may be observed in atrial tachycardia, atrial flutter and nodal tachycardia.

Treatment

The drugs of choice in the treatment of paroxysmal ventricular tachycardia are quinidine sulfate and procaine amide. These may be given orally, intravenously or intramuscularly. The dose of quinidine given orally or intramuscularly ranges from 0.2 to 0.3 Gm. four to five times per day. Sometimes, larger doses, up

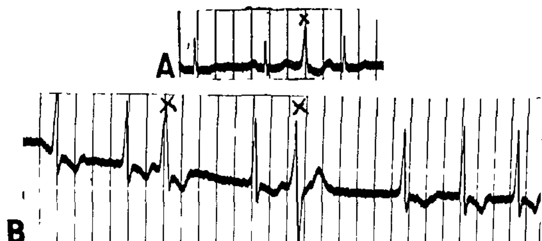
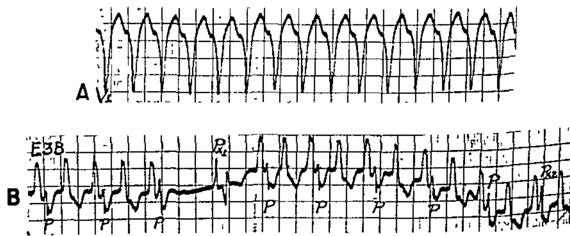


Fig 16 —Ventricular premature contractions (Vertical time lines measure 0 2 second) (A) Interpolated ventricular premature beat Note that it occurs early in diastole and does not disturb the basic rhythm The P-R interval following the ectopic beat is slightly prolonged (B) Ventricular premature beats (X) arising from different foci followed by a compensatory pause

characteristic of coupling Clinically, the coupling may be mistaken for pulsus alternans because of the alternation of weak and strong beats The difference here lies in the rhythmic irregularity due to the compensatory pauses following the extrasystoles, in pulsus alternans the rhythm is quite regular. When extrasystoles occur frequently and arise from many different foci, the rhythm is indistinguishable from that of atrial fibrillation. Most extrasystoles disappear following exercise, but occasionally they become more frequent with exercise The latter type is the more serious variety and is the result of myocardial damage The diagnosis of extrasystoles and their exact origin may be determined by electrocardiography.

Treatment

The treatment of extrasystoles is frequently rather unsatisfactory. Therapy should be directed to the underlying cause if it can be determined If some type of cardiac disease is present, improvement of the heart by rest, diuretics and digitalis may abolish the extra-



[illegible] paroxysmal tachy-
[illegible]
per minute. The P waves are easily seen and occur at the rate of 88 per minute It will be noted that none of the atrial beats are conducted except at Px_1 following a long pause Px_2 resembles Px_1 but apparently is not conducted.

two to four hours, to supplement or reinforce the action of the quinidine, especially if digitalis intoxication is suspected. Other drugs, atropine sulfate, 2 mg. hypodermically; magnesium sulfate, 15 cc. of a 20 per cent solution, papaverine, 0.2 to 0.3 Gm. every three hours, have been recommended, but we have not found these to be dependable in therapy.

Prognosis

The prognosis of paroxysmal ventricular tachycardia is extremely serious because it occurs in hearts which already are severely damaged and its duration for a prolonged period of time predisposes to ventricular fibrillation, which, as mentioned, is usually incompatible with life.

VENTRICULAR FLUTTER AND FIBRILLATION

Ventricular flutter and fibrillation are probably the most serious of the cardiac arrhythmias. Ventricular fibrillation is the terminal cardiac mechanism in a preponderant number of cases at death, it is the terminal mechanism in 50 per cent of myocardial infarctions and in most instances of digitalis toxicity. Ventricular flutter and fibrillation are analogous to the similar arrhythmias in the atria.

Etiology

The causes of ventricular fibrillation may be classified as follows

a. Drugs. Benzol, chloroform, cyclopropane, epinephrine, digitalis poisoning, quinidine, and rarely intravenous *mercurials, procaine amide* (Pronestyl), potassium, calcium chloride, Isuprel, methoxamine, norepinephrine or drugs used for angiography. These drugs produce ventricular fibrillation by one or a combination of the following mechanisms (1) toxic effect, (2) effect primarily on the metabolism of the heart muscle and (3) effect on excitability and conductivity.

b. Trauma. Severe blows to the chest; stab, arrow or bullet wounds, and intracardiac catheterization. Trauma apparently produces ventricular fibrillation by its *direct depressant* effect on the cardiac pacemakers and by causing alterations in conductivity, irritability and nutrients of the heart muscle.

c. Electrocution. Accidental or legal. This produces ventricular fibrillation by altering the irritability in conductivity.

d. Blood replacement.

e. Electrolytes. Disturbances of the potassium, sodium or calcium levels of the body may lead to ventricular fibrillation.

f. Hypothermia.

g. Following carotid sinus pressure (rare).

h. Ventricular fibrillation induced during surgery.

i. Intrinsic organic changes. Sudden occlusion of one of the coronary vessels, during a Stokes-Adams attack; and anoxia due to any cause particularly in the presence of pre-existing myocardial damage.

j. As a terminal event in patients with heart disease or other illnesses.

k. Unknown factors in apparently normal hearts. The causes of ventricular fibrillation in apparently normal hearts is not clear. Some of the factors may be: the occurrence of emotional upsets with increased secretion of epinephrine or the presence of increased irritability and vulnerability of the heart muscle. The spontaneous occurrence of ventricular fibrillation in the human subject (except as a terminal mechanism in diseased states) independent of drugs, trauma or cardiac disease, is relatively rare.

The two categories (i) and (j) include the most frequent causes of ventricular fibrillation.

Diagnosis

A clinical diagnosis cannot be made with certainty. It may be suspected when some of the etiologic factors mentioned above are present: following coronary occlusion, digitalis toxicity, the presence of complete A-V heart block with Stokes-Adams syndrome, or with syncopal attacks occurring in patients with ventricular tachycardia. It has been observed that in a patient with complete A-V heart block who develops a Stokes-Adams seizure during which the pulse rate, previously 20 to 30 per minute, jumps to 100 or more per minute, the electrocardiogram frequently shows ventricular flutter and/or ventricular fibrillation. In addition, the diagnosis should be particularly considered when there is sudden disappearance of a

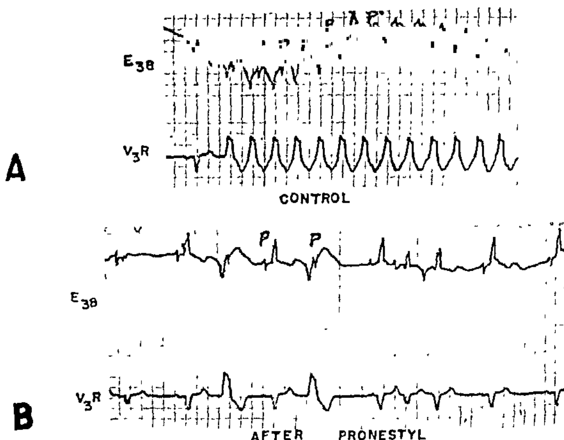


FIG 18 —Ventricular tachycardia showing retrograde conduction (A) The esophageal lead taken at the atrial level is paired with a V_3R Following a normal complex there is a run of ventricular extrasystoles constituting a paroxysm of ventricular tachycardia It will be observed in the esophageal lead (E38) that the QRS complex gives rise to a retrograde P wave and that the RP interval becomes progressively longer until one drops out at X This sequence is repeated at regular intervals This represents a reverse Wenckebach phenomenon (B) After the administration of Pronestyl, there is a return of normal sinus rhythm which is interrupted by frequent ventricular extrasystoles Note that the extrasystoles have the same configuration as the aberrant complexes of the paroxysm

to 0 6 Gm per hour, are given for 10 or more doses. The intramuscular route is used when the patient is in some degree of shock and absorption by mouth may be slow and uncertain. Occasionally, quinidine gluconate, 0 3 Gm diluted in 20 to 50 cc of normal saline solution is effective when given intravenously Quinidine acts in stopping a paroxysm of ventricular tachycardia by increasing the refractory period of the ventricle. The treatment by quinidine is effective in about one-half to two-thirds of the cases. The mistake often made is that the patient is not given enough of this drug.

Procaine amide is an extremely valuable drug in therapy. The order of dose is 0 25 to 0.5 Gm 3 to 4 times a day; the intramuscular dose is 0.5 Gm. 3 to 4 times a day or at intervals of one to two hours as indicated, the intravenous dose is 100 mg given every 3 to 4 minutes until 1 to 2 Gm. are given The parenteral administration of either quinidine or procaine amide should be monitored by the electrocardiogram (FIG 18B). Two untoward effects may occur: (a) hypotension which should be treated by the infusion of vasopressor drugs, e g , norepinephrine and (b) widening of the QRS complexes eventuating in ventricular flutter and ventricular fibrillation These may be treated by discontinuing the infusion when the QRS width exceeds 0 14 to 0 16 second, and by substituting small amounts (40 to 80 cc) of molar sodium lactate which will often reverse the QRS widening.

Potassium chloride may be used, 2 Gm every

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palpable pulse and an audible blood pressure with absent heart sounds during surgery, particularly under certain types of anesthesia. These manifestations are compatible with the presence of either ventricular fibrillation or cardiac arrest. If pounding of the chest and the use of an external pacemaker does not restore cardiac beating within a period of about 60 seconds, artificial respiration should be instituted and exploratory thoracotomy performed without delay. Upon exposure of the heart, the characteristic fibrillary twitchings become visible or the palpating hand receives the impression of "holding a bag of wriggling worms" in the presence of ventricular fibrillation The presence of cardiac arrest becomes evident on inspection or palpation The electrocardiogram will definitely establish the diagnosis, but, unfortunately, it is not always available at this crucial period

Treatment

The prophylactic treatment of ventricular flutter and fibrillation includes: (1) avoidance of the causes mentioned under etiology, (2) the use of antifibrillatory drugs during the operation at the earliest evidence of ectopic rhythms and (3) attachment of an electrocardiogram, as a monitor, and a stand-by defibrillator and pacemaker.

Active therapy consists of the following procedures (1) If cardiac beating is not restored by pounding on the chest or the use of an external pacemaker, immediate thoracotomy should be performed It is better to do an immediate thoracotomy in the face of the above findings than to wait for confirmation, (2) cardiac massage, (3) artificial respiration, (4) oxygen; and (5) blood transfusion The results of treatment are good if started within four minutes However, such complications as the return of ventricular fibrillation or cardiac arrest (temporary or permanent) may ensue. These complications may be treated as indicated above Because of the high incidence of recurrent cardiac arrest and/or ventricular fibrillation within 24 to 36 hours, it is advisable to sew a lead wire into the heart muscle before closing the chest. This is attached to the pacemaker and the patient is continually monitored. If cardiac arrest recurs, the pacemaker is automatically activated If ventricular fibrillation recurs, defibrillation is performed by the external or internal defibrillator as described above.

Treatment of Rapid Ectopic Rhythms in Absence of an Electrocardiogram

One encounters not infrequently patients with rapid ectopic rhythms, often in a severe state of heart failure, and, in the absence of an electrocardiogram, the question often arises as to the proper treatment The following summarizes the principles of therapy in those cases

1 Over 90 per cent of ectopic rhythms with rates ranging from 140 to 180 per minute are due to rapid atrial fibrillation, atrial tachycardia and atrial flutter These arrhythmias usually respond to digitalis action

2 If an electrocardiogram is not available, it must be remembered that most cases are amenable to digitalis effects and its administration may be life-saving Should the mechanism be a ventricular tachycardia, digitalis would not necessarily *be harmful but it is not to be used when the ventricular tachycardia is due to toxic digitalis effects*

3 Procaine amide (Pronestyl) and quinidine are drugs of second choice They probably should not be used in auricular fibrillation with rapid ventricular rates, especially if accompanied by shock.

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per cent ensues with well developed cyanosis, polycythemia and clubbing of the digits. A compensatory increase in cardiac output is therefore necessary to maintain body tissue oxygen delivery, and a reduction in peripheral vascular resistance allows this to occur without elevation of arterial blood pressure.

A comparable reduction in arterial oxygen delivery occurs in high altitudes (mountain sickness). The proportionate reduction in the partial pressure of oxygen associated with the low-barometric pressure results in progressively less efficient transfer of oxygen across the respiratory membranes, leading to arterial unsaturation. Compensatory responses of the body include not only those responses common to the hyperkinetic cardiovascular syndrome but also the development of polycythemia.

All forms of anemia directly reduce oxygen delivery to the tissues although the arterial blood oxygen saturation is normal. Tissue oxygenation may be partially maintained by more complete oxygen extraction from each unit of blood (increased arteriovenous oxygen difference), but the capacity of this form of compensation is extremely limited. Significant anemias (blood hemoglobin concentrations less than 8 Gm. per cent) regularly induce a high cardiac output and the other changes of the hyperkinetic cardiovascular syndrome.

The increased metabolic rate in hyperthyroidism carries with it circulatory requirements which are comparably increased. The increased cardiac output is mediated primarily by an accelerated heart rate with little change (or an actual decrease) in stroke volume. This tachycardia appears to be produced in part by the metabolic derangement in the sinus node and the moderator reflex system and is not in its entirety due to the hyperkinetic cardiovascular syndrome.[15]

Not so well understood is the need for a high-blood tissue oxygen gradient in thiamine deficiency states ("beriberi heart"). A severe chronic vitamin B deficiency may be reflected in inefficient metabolism due to an intracellular respiratory enzyme deficiency state. This wasteful metabolism requires an increased oxygen supply and therefore an increased cardiac output. The direct effect of the metabolic abnor-

TABLE 1.—*Etiology of Chronic Circulatory Insufficiency*

	Increased venous pressure	Cardiomegaly	Cardiac output	Peripheral vascular resistance
Myocardial disease	yes	yes	decreased	increased
Valvular insufficiency	yes	yes	decreased	increased
Circulatory obstruction				
precardiac	yes	no	decreased	increased
cardiac (valvular)	yes	yes	decreased	increased
postcardiac (hypertension)	yes	yes	decreased	increased
Hyperkinetic Cardiovascular Syndrome	yes	yes	increased	decreased

TABLE 2.—*Etiology of the Hyperkinetic Cardiovascular Syndromes*

DISCRETE ARTERIOVENOUS FISTULAE
Traumatic A-V fistula
Congenital single and multiple A-V fistulae
Pregnancy
Paget's disease of bone
Hereditary telangiectasia
Laennec's cirrhosis
Vascular tumors
Toxic goiter (local changes)

GENERALIZED REDUCTION IN ARTERIOLAR RESISTANCE ("FUNCTIONAL A-V FISTULA")
Anoxemia
- respiratory factors
  - decreased O_2 tension in inspired air
  - deficient alveolar ventilation
  - deficient O_2 transfer across alveolar-capillary membranes
  - pulmonary A-V shunts
- reduction in functioning hemoglobin concentration
  - anemic states
  - abnormal nonfunctioning hemoglobin compounds
    - methemoglobinemia
    - carbhemoglobinemia
    - sulfhemoglobinemia

Increased tissue circulatory requirements
- increased metabolic rate
  - hyperthyroidism
- decreased metabolic efficiency
  - thiamine deficiency (beriberi heart)

The Hyperkinetic Cardiovascular Syndrome

By JOHN H. HUSTON, M.D., AND FRANCOIS M. ABBOUD, M D

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THE hyperkinetic cardiovascular syndrome is a term applied to those conditions of different etiologies but with common hemodynamic features consisting of an increased cardiac output, a decreased peripheral vascular resistance and an increased rate of venous return. The manifestations include a bounding pulse, tachycardia, distended superficial veins and warm flushed skin. The hyperkinetic cardiovascular syndrome may cause pathophysiologic changes simulating congestive heart failure or more commonly may precipitate or aggravate congestive heart failure in the presence of existing heart disease TABLE 1 outlines the various causes of chronic circulatory insufficiency and illustrates the fact that this hyperkinetic syndrome differs from the other causes by virtue of its increase in cardiac output along with a decrease in peripheral vascular resistance. A classification of the conditions which cause the hyperkinetic cardiovascular syndrome is presented in TABLE 2

The circulatory insufficiency may be *relative* as in anemia with decreased oxygen carrying capacity or in hypermetabolism with increased tissue requirements, or *absolute* where fistulous arteriovenous connections allow large amounts of arterial blood to bypass the body tissues

Traumatic arteriovenous communications differ in pathogenesis and certain clinical manifestations from the other causes of the hyperkinetic syndrome. The site of communication is between large vessels rather than capillaries. Such a communication results in an abrupt fall in peripheral resistance which in turn results in a decrease in arterial blood pressure and an increase in blood flow.

In addition to the hyperkinetic syndrome, an interesting local sequence of events follows the development of a large localized A-V fistula of an extremity.[5] The fistulous opening is marked by a coarse machinery murmur and thrill with local pulsation of arteries and veins The local increase in venous pressure blocks venous return from the more peripheral portions of the extremity, while its arterial supply largely disappears through the shunt. A cold, edematous limb results which occasionally succumbs to gangrene As time allows compensatory adjustments to develop, the arteries and veins about the lesion become dilated, tortuous and thin-walled Some retrograde blood flow to the limb occurs through the affected veins, and considerable collateral venous return develops The limb then becomes hypervascular. Unsightly hypertrophy often follows

The localized lesions found in Paget's disease of bone occurring at the capillary level are occasionally overlooked causes for large arteriovenous shunts[14] This condition is often confused with arteriosclerotic cardiovascular disease because of its common association with calcification of the arteries (Monckeberg type), cardiac valve rings and interventricular septum to produce atrial or intraventricular conduction defects[10]

The circulatory effects of pregnancy include considerable increases in blood volume, a rise in oxygen consumption and a physiologic uterine arteriovenous fistula These factors are associated with increases in cardiac output of up to 50 per cent[1, 12] The ease with which the heart meets these temporarily increased flow requirements (often in spite of severe valvular deformities) testifies to the tremendous reserve of the heart muscle

Pulmonary arteriovenous fistulae allow large amounts of venous blood to bypass the respiratory membranes A consequent depression of arterial oxygen saturation to levels of 70 to 75

per cent ensues with well developed cyanosis, polycythemia and clubbing of the digits. A compensatory increase in cardiac output is therefore necessary to maintain body tissue oxygen delivery, and a reduction in peripheral vascular resistance allows this to occur without elevation of arterial blood pressure.

A comparable reduction in arterial oxygen delivery occurs in high altitudes (mountain sickness). The proportionate reduction in the partial pressure of oxygen associated with the low-barometric pressure results in progressively less efficient transfer of oxygen across the respiratory membranes, leading to arterial unsaturation. Compensatory responses of the body include not only those responses common to the hyperkinetic cardiovascular syndrome but also the development of polycythemia.

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    - carbhemoglobinemia
    - sulfhemoglobinemia

Increased tissue circulatory requirements
- increased metabolic rate
  - hyperthyroidism
- decreased metabolic efficiency
  - thiamine deficiency (beriberi heart)

mality on heart rate and myocardial contractility and irritability may obscure the basic hyperkinetic cardiovascular response. Either or both may aggravate the underlying heart disease and give rise to severe congestive heart failure and cardiac arrhythmias [13]

Physiologic adjustments in the hyperkinetic cardiovascular syndrome are more interrelated than sequential (Fig 1). Disturbances in both the arterial and the venous "compartments" initiate multiple neural, humoral and hemodynamic reflexes simultaneously. These reflexes induce an adequate blood pressure level in the face of a decreased peripheral vascular resistance and an increased cardiac output (pressure is proportionate to cardiac output times peripheral resistance).[20] Thus, a decrease in arterial blood pressure is detected (carotid and aortic bodies) and immediately opposed by a reflex tachycardia mediated by the cardiac moderator nerves (Marey's law of the heart, Branham's sign of peripheral arterial venous fistula) Such a "first line of defense" is most commonly seen in acute reductions of peripheral vascular resistance (e g., exercise, febrile states) before other homeostatic changes have had time to become effective [17] As the peripheral circulatory abnormality becomes chronic (chronic anemias, high-altitude acclimatization), the cardiac output and blood pressure can usually be maintained by the development of an increased stroke

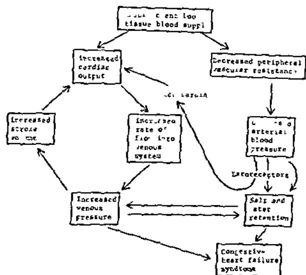


Fig. 1.—Circulatory adjustments in the hyperkinetic cardiovascular syndrome.

volume so that tachycardia is no longer required

The same pressure sensors that initiate reflex tachycardia may be part of the elusive "volume receptor system" and may initiate sodium and water retention by a neurohemoral effect on the kidneys.[2] A diversion of renal blood flow (which usually amounts to one-third of the cardiac output) to the other body tissues is a more readily demonstrated cause for salt and fluid retention The increase in blood volume resulting from minor degrees of fluid retention tends to increase venous pressure slightly and insure maximal diastolic ventricular filling [9,19] Thus, it is possible to maintain an increasing stroke volume up to a limit. As the capacity of the ventricular cavities increases, the systolic tension developed within their walls must also increase if ejection pressure is to be maintained (LaPlace principle) * This increasing tension requirement both limits the maximal possible increase in heart size and serves as a stimulus for some true myocardial hypertrophy.[4] A superficially adequate circulation with a normal heart rate at rest is usually achieved by these mechanisms, but an inadequate circulatory response to any further increase in tissue demands usually produces symptoms In the presence of associated heart disease, a circulatory system able to cope with either the hyperkinetic syndrome or the heart disease may fail in the presence of both.

Clinical recognition of the hyperkinetic cardiovascular syndrome is dependent on the suspicion and detection of an increased cardiac output in the presence of mild cardiorespiratory complaints or signs of venous congestion [19]

An inability to increase cardiac output further (reduced cardiac reserve) is the basis for the usual presenting complaints of prolonged breathlessness, tachycardia and weariness following exertion These symptoms are not specific and are common to heart failure in general and to certain anxiety states.

Some venous engorgement without edema or

* LaPlace principle adapted to a cylinder $T = P \times R$, where T = tension within the cylinder wall, P = pressure of the contained fluid, and R = the radius of curvature of the cylinder (a measure of volume of the ventricular "cylinder").

liver enlargement may also accompany the hyperkinetic cardiovascular syndrome and make one consider the presence of more severe disease. Although the rapid blood flow through the venous system suggests a rather high driving pressure, the venous pressures seldom reach levels commonly observed in frank congestive heart failure, and fluid retention may be clinically detected only by a prompt but temporary response to diuretic administration

Cardiomegaly is not marked and disproportionate chamber enlargement does not occur. The heart size actually reflects the increased diastolic capacity required for an increased stroke volume and its appearance is more that of cardiac "dilatation" than "hypertrophy." So long as the enlarging heart is able to maintain a normal systolic ejection pressure without marked elevation of venous pressure, this cardiomegaly may be regarded as a benign physiologic change

The increased pulsations of the overactive heart may be detected by simple observation and palpation, and by fluoroscopic inspection of the cardiac borders The increased systolic flow through the aortic and pulmonic valves regularly produces functional heart murmurs superficially suggestive of valvular stenosis[11] A murmur of functional mitral insufficiency is also occasionally audible during early systole. This is apparently due to excessive chorda tendinal tension (from ventricular enlargement) which delays mitral valve closure at the onset of systole[16]

Peripheral signs of an increased stroke volume include a large arterial and capillary pulsation The arterial systolic pressure is normal or slightly elevated while the diastolic pressure is abnormally low The increased blood flow rate often results in puzzling localized arterial and venous murmurs This increased circulatory velocity is easily confirmed by the intravenous injection of ether or Decholin. A normal or shortened arm-to-lung (ether)* or arm-to-tongue (Decholin)† circulation time tends to exclude other organic causes for congestive failure. The x-ray examination often discloses increased pulmonary vascular markings with a suggestion of "hilar dance" in addition to an overactive, slightly enlarged heart The electrocardiogram is not distinctive and is often within normal limits. Sinus tachycardia, nonspecific repolarization changes and mild intraventricular conduction defects are occasional abnormalities.

The hyperkinetic cardiovascular syndrome is frequently suggested by an anxiety state with cardiac and respiratory symptoms.[19] The pattern of dyspnea is usually of differential value. In anxiety states, dyspnea is not solely exertional, and is not relieved (but is increased) by voluntary hyperventilation. Profuse sweating from the axillae, with cold sweaty palms and soles favors the diagnosis of anxiety state and is in marked contrast to the warm skin of the individual with the hyperkinetic cardiovascular syndrome Palpitation, increased blood pressure, increased pulse pressure and tachycardia are usually labile in anxiety states rather than chronic. Complaints of atypical chest pain, fatigue, dizzy spells (or actual syncope) and functional disturbances of other systems complete the clinical picture of the cardiac neurotic.

In the management of the hyperkinetic cardiovascular syndrome, the functional integrity of the myocardium must be recognized in spite of the peripheral circulatory findings that may suggest primary heart disease. Recognition and correction of the specific abnormality responsible for the noncardiac cause of the circulatory insufficiency is necessary if permanent improvement is to be expected

The hyperkinetic cardiovascular syndrome most often presents as a complication of some other cardiac disease and may be the precipitating factor of acute or chronic congestive heart failure. In this situation, the usual treatment for heart failure may be disappointing since digitalis, diuretics and restriction of sodium do not significantly affect the abnormal demands of the hyperkinetic cardiovascular syndrome Correction of anemia or hyperthyroidism may induce surprising reversal of the

* Arm-to-lung circulation time (ether) dosage—approximately $\frac{1}{4}$ cc of ethyl ether in $\frac{1}{2}$ cc saline, normal range—4 to 8 seconds, end point—cough, ether taste or smell

† Arm to tongue circulation time (Decholin) dosage—5 cc of 20 per cent solution of Decholin, normal range—10 to 16 seconds; end point—grimace, bitter taste.

congestive state.[8] A contributory cause for the increased myocardial and tissue circulatory demands may be the malnutrition which insidiously develops with progressive heart failure Recognition that thiamine depletion with cellular respiratory enzyme insufficiency is prone to occur in congestive heart failure suggests a more common use of this dietary supplement (especially thiamine) even though a clear-cut clinical deficiency is not demonstrated [13]

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Chronic Congestive Heart Failure

By E. E. EDDLEMAN, Jr., M.D.

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CONGESTIVE heart failure is a clinical syndrome manifested by circulatory congestion without specific etiology. It may result from myocardial weakening, mechanical heart diseases, or from a combination of both. This may be expressed in a somewhat different manner in that congestive heart failure can result from a defect in ventricular emptying, a defect in ventricular filling or a combination of both. Thus, myocardial failure exists when there is an abnormal or inappropriate increase in end-diastolic volume for a given stroke volume. Failure due to mechanical heart disease results from the obstruction of blood flow into or within the heart, which leads to a decreased cardiac output, and to either pulmonary or systemic venous congestion. The two processes may also coexist. A classification based on these definitions is presented in TABLE 1 In addition, certain classifications such as forward or backward failure have been applied, as well as right-sided and left-sided congestive heart failure Both of these classifications of congestive heart failure have merit only in the clinical considerations of the disease.

PHYSIOLOGIC CONSIDERATIONS OF PRIMARY MYOCARDIAL FAILURE

Primary myocardial failure occurs when there is an abnormal increase in end-diastolic volume per given stroke volume (defective systolic emptying) * This is best explained by an analysis of the changes that occur when the heart goes into failure In a weakened heart, an increased stretch of the myocardium is necessary in order to achieve a given output. TABLE 2 illustrates the theoretical sequence of changes, beat by beat, during the development of heart failure. In order to augment the stroke volume in the failing heart, it is necessary that the end-diastolic volume be increased over that noted in the normal heart. It should be pointed out that one major way by which stroke volume can be elevated and more energy released is by an increase in force of contraction as the result of dilatation or stretch of the muscle fibers A failing heart differs from a normal heart only in that less energy and force are released per given stretch, under comparable conditions Therefore, the efficiency of a failing heart is reduced. A point is reached when the stroke volume is unable to increase further even with a still larger end-diastolic volume. Subsequently, there may be a decrease in stroke volume. This discussion merely restates the principles that have been known for years, primarily from the work of Starling [21] Although Starling originally expressed the function curve of the heart in stroke volume (since resistance was kept constant this is equivalent to stroke work) with respect to end-diastolic volume, many other parameters have been used in defining cardiac function Thus, the Starling principle now is generally regarded as a broad concept without specific regard for the units used. As this has led to some confusion as to validity of the principle, some further discussion of various physiologic parameters appears appropriate

Ventricular End-Diastolic Pressure

Ventricular end-diastolic pressure is not synonymous with end-diastolic volume Therefore, there may not be a correlation with pressure and stroke volume or stroke work since the pressure-volume relationships of the human ventricle have never been clearly elucidated. This relationship must be considered in any interpretation, since significant changes in ventricular volume may occur without an ap-

* It is understood that stroke volume is not the parameter that is primarily determined by the stretch. However, the principle is similar regardless of the exact parameter used

congestive state[8] A contributory cause for the increased myocardial and tissue circulatory demands may be the malnutrition which insidiously develops with progressive heart failure Recognition that thiamine depletion with cellular respiratory enzyme insufficiency is prone to occur in congestive heart failure suggests a more common use of this dietary supplement (especially thiamine) even though a clear-cut clinical deficiency is not demonstrated.[13]

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give measurements within the range of experimental error. Nevertheless, there is always some rise either in atrial or end-diastolic-ventricular pressure with all types of heart failure, and the increase in pressure in either the pulmonary or systemic vascular beds is a major factor in the production of symptoms. The rise in pressure (either ventricular or atrial) is a result of the physiologic alterations. Thus, pressure and stroke volume studies alone cannot be interpreted as evidence for or against the Starling concept.

Relation of Heart Rate to Stroke Volume

In most heart-lung preparations, the heart rate is kept constant, and therefore its influence is not a factor in the interpretation of the function curves. In the intact subject, the effect of changes in heart rate is important, especially during exercise. Studies concerning the changes of stroke volume and end-diastolic volume in the intact dog have shown that with the experimental animal the cardiac output is increased in response to exercise primarily by an increase in heart rate.[18] Thus, very little if any change occurs in the stroke volume. This has been interpreted as indicating the heart does not respond according to the Starling principle. These data cannot be applied directly to man, since it is well established that exercise in the upright position is accompanied by important increases in stroke volume as well as in increased heart rate.[11, 22] The physical fitness of the individual also influences these relationships, since the trained athlete responds to a given exercise with a slower heart rate and a greater stroke volume than do untrained individuals.[18] This difference in major part is a reflection of the increased circulating blood volume and red cell mass resulting from physical training.[20] Recent confusion has arisen apparently from a failure to recognize the importance of body position in determining the resting venous return. When a subject is supine, the venous return is near maximum and is little affected by exercise. Even in this position, however, studies of multiple levels of exercise in the same individual reveal a strong trend toward important increases in stroke volume at one or more levels of exercise.[15]

The Influence of Myocardial Contractility

Although physiologic data on myocardial contractility have been available for some time, the significance of myocardial contractility has had little emphasis. It is well known that the heart can change the force of contraction even with a constant end-diastolic volume as the result of other factors. Catecholamines increase contractility, as does the stimulation of the cardio-accelerator nerves, whereas vagal stimulation depresses contractility. Thus, in the intact subject, contractility may be variable and lead to data which are difficult to interpret. The intact human or the intact dog is an exceedingly complex system, and there are many factors which can influence the cardiac output, all of which are operative at the same time. For instance, heart rate, physical training, the state of the peripheral resistance, the influence of the autonomic nerves (which increase myocardial contractility) and the innate contractility of the myocardium itself are some factors. Thus, the Starling principle probably is still valid if the variables mentioned could be properly equated or adjusted to a common base line. It is quite likely that myocardial contractility, which cannot at the present time be measured in living man, is a most important factor. Therefore, it is impossible to compare on a function or Starling curve one subject to the other and even a single heart to itself under conditions where contractility may be altered.

Sarnoff and his group have recently reinvestigated the problem of ventricular function and have brought out many other points.[1, 5, 9, 19] The importance of the various factors in determining the stroke volume and stroke work has been well elucidated. One of the differences in Sarnoff's data from that obtained by Starling would indicate that there is no true descending limb to the Starling curve but a curve which plateaus in the normal dog when the pericardium is intact. It should be mentioned that this variation does not refute the principles involved. From a theoretical consideration (TABLE 2), it is apparent that heart

TABLE 1.—*Physiologic Classification of Congestive Heart Failure**

I. PRIMARY MYOCARDIAL FAILURE
[Defective ventricular emptying (an increase in end-diastolic volume without an appropriate rise in stroke volume)]

Coronary heart disease
Senile heart disease
Hypertensive cardiovascular disease
Myocarditis
- rheumatic
- viral
- miscellaneous

Certain congenital heart defects
- intraventricular septal defect, etc.

Vascular overload
Arteriovenous fistulas
Metabolic heart disease
- beriberi heart disease
- myxedema heart disease
- thyrotoxic heart disease

Certain valvular heart diseases
- aortic stenosis
- aortic insufficiency
- mitral insufficiency
- tricuspid insufficiency
- pulmonic stenosis

II. MECHANICAL HEART FAILURE
[Defective ventricular filling (intracardiac obstruction to ventricular filling resulting in an increased vascular pressure proximal to the obstruction)]

Mitral stenosis (in the absence of right ventricular myocardial failure)
Tricuspid stenosis

III. COMBINED MECHANICAL AND MYOCARDIAL HEART FAILURE
[Defective ventricular filling and emptying (obstruction to ventricular filling is combined with an end diastolic volume disproportionately high in relation to stroke volume)]

Constrictive heart disease
- constrictive pericarditis
- constrictive endocarditis (fibroelastosis)

Scleroderma heart disease
Amyloid heart disease

* This classification is intended to show only examples as to how heart failure may be physiologically classified.

A somewhat similar classification of heart failure has been previously discussed by BURWELL, C. S.: Med. Clin. N. Am. *12*: 1197, 1929.

preciable rise in end-diastolic ventricular pressure. The theoretical pressure volume curve *of the ventricle* is illustrated in FIGURE 1. As the volume of the ventricle initially increases there is very little pressure rise. As the elastic limit of the myocardium is reached, small changes in volume should result in large changes in pressure. It is true, however, that there is probably some rise in pressure when the volume is increased, but the change at the lower end of the curve may be so small as to

TABLE 2.—*Theoretical Sequence of Events in the Development of Myocardial Failure (Defective Systolic Ventricular Emptying)*

	End-diastolic Volume cc		Stroke Volume cc		Residual Ventricular Volume cc	
	Normal	Failing	Normal	Failing	Normal	Failing
1	80	80	70	70	10	10
2	84	84	73	72	11	12
3	88	88	76	74	12	14
4	92	92	79	76	13	16
5	96	96	82	78	14	18
6	100	100	85	80	15	20
7	104	104	88	80	16	24
8	108	108	91	80	17	28
9	112	112	94	78	18	34
10	116	116	97	76	19	40
11	120	120	100	74	20	46

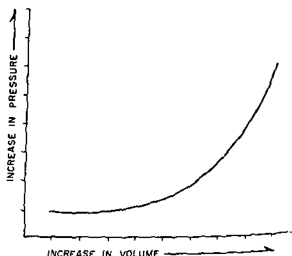


FIG. 1.—Demonstration of the general characteristics of the pressure volume relationships of an elastic structure such as the human ventricle. Note that large changes in volume at the lower end of the curve are accompanied by a small increase in pressure, whereas near the elastic limits of the heart marked changes in pressure results from a small increase in volume. Thus, the pressure volume relationships of the human ventricle are probably not linearly correlated.

the end-diastolic volume of either the left or right ventricle. Even though the clinical picture resembles that due to left ventricular failure, the cause is purely mechanical in origin. The stenotic mitral orifice simply results in a "damming up" of blood in the left atrium and pulmonary vascular bed, and at the same time prevents adequate left ventricular filling with a resulting decrease in left ventricular output. The "damming up" results at first in an appreciable increase only in the *volume* of the left atrium and pulmonary vascular bed, but with further increase in volume the *pressure* in the left atrium and pulmonary vascular bed also increases to give the picture of pulmonary vascular congestion. Whether or not this type of pulmonary vascular congestion should actually be classified as heart failure is still controversial. Nevertheless, the symptoms are identical to congestive failure and can be regarded as such. Thus, the primary trouble is the mechanical obstruction to the flow of blood at the mitral orifice. The mechanical obstruction in turn may lead to increased right ventricular work, with dilatation, and finally right ventricular myocardial failure. The right ventricular failure then is manifested by systemic venous congestion; only then can the definition as related to end-diastolic volume be applied. Although aortic stenosis constitutes an intracardiac obstruction, it is not analogous to mitral stenosis since the congestive failure probably results from an inordinate increase in end-diastolic volume of the left ventricle in relation to the stroke volume (defective emptying). The congestive heart failure of aortic stenosis, therefore, falls into the first category of primary myocardial failure

The congestive failure of tricuspid stenosis (or other type of obstructing lesion of the great veins or right atrium) represents right-sided mechanical heart failure Here the "damming up" of blood takes place behind the stenotic tricuspid orifice (or in the left atrium or great veins in the case of a higher obstruction) with a resulting increase first in systemic venous volume and later systemic venous pressure. The defective filling of the right ventricle is the result of the obstruction, and myocardial failure does not ensue.

Combined Mechanical and Myocardial Heart Failure

Table 1 lists some of the cardiac diseases which may result from a combination of defective ventricular filling and defective emptying. The constrictive heart diseases have a limitation to filling, but the ventricle in turn cannot empty properly because of the constriction. Both factors may be present equally, or either one may predominate in a given patient. Congestive heart failure, in these instances, can occur with a small ventricular end-diastolic volume when mechanical factors dominate or with a large end-diastolic volume where myocardial failure is of greater significance. In the case of mitral stenosis with resultant right ventricular failure, the pulmonary vascular congestion and elevated left atrial pressure are the result of mechanical obstruction at the mitral orifice, whereas the systemic vascular congestion and elevated right atrial pressure are the result of right ventricular myocardial failure.

Metabolism of the Failing Heart

Since myocardial failure results from the weakening of the heart muscle, considerable attention has been given to the possible alterations in metabolism which may lead to a decrease in contractility or in the strength of contraction. Only two types of heart disease have thus far been shown to be associated with abnormal heart muscle metabolism· beriberi and myxedema.* In all other forms of congestive heart failure the myocardium exhibits normal metabolic pathways for glucose, fat and protein.[3] The only defect so far encountered is a decreased efficiency of the muscle rather than alteration in the handling of the various metabolites. In most types of congestive heart failure, therefore, the changes as noted in disturbances of metabolism usually are more subtle than can be detected by our present somewhat crude technics. It is indeed possible that defects could occur in the contractile proteins or even in the transfer of metabolites across the cellular membrane. Moreover, the catecholamines in the myocardium may be

* Thyrotoxic heart disease may be a third type

failure may still occur even though the stroke volume does not diminish with an increase in diastolic volume If the stroke volume is not as predicted for a given diastolic volume, failure is present even though the stroke volume does not decline. Thus, when the cardiac output (stroke volume) is not increased proportionately along the theoretical line per given increase in diastolic volume (Fig 2), the heart still can be regarded as failing, even though the cardiac output does not diminish In other words, the heart can be in failure on the *ascending limb* of the curve if its response decreases below that predicted. In addition, Sarnoff has pointed out that there is no single Starling curve or function curve that can fit all situations This is probably due to the variations in myocardial contractility encountered, a possibility recognized by Starling

Thus, the basic definition of myocardial failure still involves an increase in end-diastolic volume out of proportion to the output or in other words defective *systolic emptying*. The definition of congestive heart failure as an "inadequate cardiac output in relation to

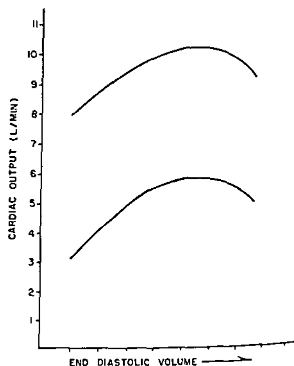


Fig 3 —Presentation of two Starling-type curves set at different levels of cardiac output. They illustrate the fact that failure can occur regardless of the absolute level of cardiac output *Theoretically*, the upper curve applies to thyrotoxic heart disease, while the lower curve applies to low output failure

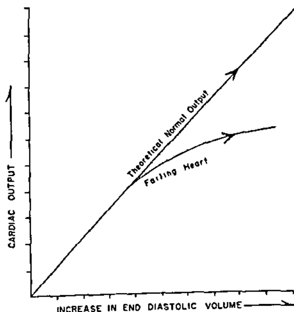


Fig 2 —Theoretical curve demonstrating that failure can occur even without a descending limb on the function curve. Note that if the output of a heart is below that anticipated under comparable conditions, then the heart can be considered to be failing. Thus, the ventricles can fail on the ascending limb of the function curve

peripheral oxygen or metabolic demands" cannot be applied universally, since the congestive failure which results from vascular overload is an exception which does not fit this definition Nevertheless, the peripheral demands probably are important in many types of congestive failure in that they may help determine the level of the cardiac output. This is particularly evident in thyrotoxic heart disease Nevertheless, a thyrotoxic patient even in the absence of other heart disease may develop myocardial failure which may progress to congestive failure when there is an increase in diastolic volume per stroke volume even though cardiac output may be considerably elevated at the time (Fig 3)

Physiologic Considerations of Mechanical Heart Failure

Mechanical heart failure as listed in Table 1 obviously does not fit the physiologic considerations first presented. Mitral stenosis uncomplicated by right ventricular myocardial failure probably does not have an increase in

muscle apparently is a syncytium of muscle fibers. Early studies of the anatomists indicate that the right ventricular muscle is continuous with the muscle of the left ventricle.[15,17] This has been recently challenged by Grant in that he describes the right ventricle as an appendage attached to the left.[7] At present, it is impossible to determine whether or not all these factors are operative or which one is most important. In any event, it is undoubtedly true that the right ventricle certainly can fail as a result of left ventricular failure. Again, mechanical obstructive phenomena can result in a combination of left-sided and right-sided congestive failure. In fact, the constrictive diseases (constrictive endocarditis and pericarditis) are frequently associated with both right-sided and left-sided congestive phenomena, although right-sided failure is more common. The converse as to whether the left ventricle can fail as a result of right ventricular failure has never been satisfactorily explored

Mechanism of Signs and Symptoms

Exertional Dyspnea

The predominant cause of the symptom associated with left ventricular failure is pulmonary congestion as a result of an increase in left ventricular end-diastolic volume and pressure, left atrial and pulmonary venous volume and pressure, and pulmonary capillary volume and pressure with or without transudation of fluid across the capillaries into the alveoli Exertional dyspnea is a manifestation of pulmonary congestion that occurs only on effort. This is the best example of "backward" heart failure Since heart failure is associated with an increase in intravascular blood volume, there may be an accentuation of the process with exaggeration of the above sequence of events It should be noted that the transudation of fluid does not have to occur entirely into alveolar space but may be interstitial. Some patients may not develop moist pulmonary rales but nevertheless have an increase in the fluid content in the interstitial spaces If the degree of fluid accumulation is sufficient, whether it be interstitial or intra-alveolar, impaired alveolar-capillary diffusion of oxygen ensues; however, desaturation does not account for the shortness of breath, since normal subjects who breathe low oxygen mixtures producing comparable desaturation of arterial blood do not develop a similar degree of dyspnea Although the dyspnea from left-sided congestive failure is due to pulmonary congestion, the exact mechanism by which the sensation of dyspnea is produced is still unknown. It is presumed to be due to reflexes arising from the presence of the congestion or distention of the pulmonary parenchyma, like that noted in patients with uncomplicated lobar pneumonia. It is also possible that the altered compliance and an increased work of breathing produced by the more rigid congested lungs may be factors A decreased tissue oxygen tension may also play a part in the symptom complex.

Paroxysmal Nocturnal Dyspnea

Paroxysmal nocturnal dyspnea occurs from an exaggeration of the phenomena described above with transudation of fluid across the alveolar membrane. The usual explanation for the occurrence at night is presumed to be related to the postural change of the patient. When in the upright position, the intravascular fluid compartment is expanded primarily in the lower extremities, and, when recumbent, this fluid is mobilized with the expansion of intravascular blood volume A greater load for the left ventricle occurs leading to pulmonary congestion.

Cardiac Asthma

Cardiac asthma is the clinical syndrome in patients with left-sided congestive failure in whom the manifestation of pulmonary edema is wheezing.[11] It is due apparently to narrowing of the bronchioles by edema or to a reflex spasm of the bronchial musculature It is often difficult to distinguish cardiac asthma from true bronchial asthma and can be done only if the possibility of left ventricular failure is constantly kept in mind.

Acute Pulmonary Edema

Acute pulmonary edema represents a prolonged or an exaggerated episode of pulmonary

decreased with congestive failure Recent studies have shown that actomyosin threads prepared from failing hearts have diminished contractility compared to those obtained from normal hearts [10] The reasons for this change are unknown at present, and the exact role of actomyosin in the mechanism of failure is obscure Although it does appear reasonable that abnormalities in either myocardial metabolism, contractile proteins or cellular permeability should occur in congestive failure, little information is available as to the nature of these abnormalities.

Clinical Syndromes Associated with Congestive Heart Failure

The clinical classifications of disease as presented in Table 3 are based only on the clinical manifestations of the disease and *not on* the physiologic definition. For example, left-sided congestive failure due to hypertension,

Table 3.—*Clinical Classification of Congestive Heart Failure**

I. Left-Sided Congestive Failure (Pulmonary Congestion)
- Myocardial—defective ventricular emptying (coronary heart disease, hypertension, aortic valvular disease, myocarditis, etc)
- Mechanical—defective ventricular filling valvular (mitral stenosis)
- Combined myocardial and mechanical (constrictive pericarditis, endocardial constriction, amyloid heart disease, etc)

II. Right-Sided Congestive Failure (Venous Congestion)
- Myocardial—defective ventricular emptying (pulmonic stenosis)
- Mechanical—defective ventricular filling (tricuspid stenosis)
- Combined myocardial and mechanical (constrictive pericarditis, endocardial constriction, amyloid heart disease, etc)

III Left- and Right-Sided Congestive Failure (Pulmonary and Venous Congestion)
- Myocardial (myocarditis)
- All combined myocardial and mechanical heart diseases
- Right-sided failure as the result of left-sided failure

* This table is intended only to show examples as to how heart failure may be clinically classified and does not include all examples or causes

aortic stenosis, aortic insufficiency and coronary heart disease obviously fits the physiologic definition and produces the well appreciated clinical syndrome of dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, and acute pulmonary edema However, most of these clinical features may be seen with constrictive heart disease either of the endocardium, myocardium or pericardium, and in patients with mitral stenosis Obviously, congestive phenomena due to mitral stenosis are clinically similar to those of left ventricular failure but are not the result of an increase of end-diastolic volume out of proportion to cardiac output A similar analogy applies to the syndromes associated with right-sided congestive heart failure, since the manifestations of an increase in venous pressure, venous distention, enlargement of the liver, pedal edema or ascites may be due either to failure of the right ventricle or mechanical phenomena, such as endocardial, myocardial or pericardial constriction, or tricuspid stenosis

Frequently, manifestations of both left-sided and right sided failure occur in the same patient. The most common cause of right-sided congestive failure is left-sided congestive failure, however, the mechanisms for this are still somewhat obscure The sequence of events usually described includes (a) an increase in diastolic volume of the left ventricle, (b) a rise in left ventricular diastolic pressure; (c) an increase in volume and pressure in the left atrium; (d) a rise in pulmonary venous and capillary volume and pressure, (e) a rise in pulmonary artery pressure; and (f) an increase in right ventricular work with resulting dilatation, and failure of the right ventricular myocardium Although this sequential process undoubtedly contributes to the development of right-sided failure secondary to left, there are probably other factors involved, since the pulmonary artery pressure may be disproportionally elevated over that of the pulmonary capillary pressure, suggesting that reflex arteriolar constriction may be responsible for the disproportionate elevation of the pulmonary artery pressure. The anatomic relationship of the right ventricular muscle to that of left ventricle may be a factor since the heart

has occurred with relatively high glomerular filtration rates Patients have been studied in whom serial measurements of the glomerular filtration rate did not parallel the presence or absence of edema[18] Some patients may show no edema despite a very low glomerular filtration rate, and conversely patients with only slightly reduced glomerular filtration rates may exhibit edema. However, if the glomerular filtration rate is reduced to a critical level (approximately 70 ml per minute) almost total tubular reabsorption of sodium will result. The level of the glomerular filtration rate is a factor in sodium retention in congestive failure, however, the critical determinant still appears to be related to *tubular reabsorption of sodium*

Increased venous pressure. The classic concept has held that the increase in venous pressure opposes the oncotic pressure at the distal end of the capillary, thus preventing the filtered fluid from returning to the intravascular compartment This is a very important mechanism in determining the location of edema fluid but probably does not influence the actual development of edema There are many instances in which a marked increase in venous pressure occurs without edema formation (when the intravascular fluid compartment is not expanded), this can be noted in patients in whom the inferior vena cava has been ligated All of these patients do not develop edema of the lower extremities, even though there is marked elevation of the venous pressure below the occlusion. Nevertheless, the increase in venous pressure in patients with congestive failure does determine the location of the edema fluid Since orthopnea is frequently present in congestive failure, these patients remain in the upright position, with their feet in the dependent position. Thus, the edema fluid usually *collects in the lower* extremities and abdomen The few patients who do not have orthopnea collect edema fluid periorbitally, and in the upper extremities as well In addition to the venous pressure determining the location of the edema fluid, an increase in venous pressure per se has been demonstrated in experimental animals to promote tubular reabsorption of sodium[4] How much this contributes to the over-all sodium retention and edema formation is at present unknown.

Aldosterone. It has been pointed out that all edematous states are associated with an increase in aldosterone excretion in the urine, and this has led to the hypothesis that the elevated aldosterone secretion in patients with congestive heart failure promotes tubular sodium reabsorption and may contribute to the formation of edema At present, it is unknown whether the aldosterone is primarily elevated resulting in edema formation or whether it is only a secondary phenomenon and of no pathogenic significance. It is quite possible that aldosterone does play some part in edema formation, however, instances have been encountered in which the aldosterone secretion was markedly elevated and subsequently depressed to zero by amphenone without any loss of edema fluid[8] Thus, aldosterone is not the sole answer as to the mechanism of edema formation Still more difficult to explain are the factors which result in the increased secretion of aldosterone in these patients Restriction of sodium certainly is a stimulus for aldosterone excretion, and it is possible that some of the elevated values reported are simply the result of sodium restriction in cardiac patients.

Increased excretion of antidiuretic hormone secondary to stimulation of the osmotic receptor center Water can be retained secondarily to the retention of sodium through the activation of the osmoreceptor center. However, this probably plays only a secondary role in patients with congestive heart failure and is probably not responsible for the edema formation A clinical situation in which an antidiuretic-like substance does play an important role in water retention is refractory congestive failure when water retention may become a primary feature of the disease In the usual patient, water retention is only passive, and if one regulates the sodium excretion or sodium intake, no control of the fluid intake is necessary Therefore, fluid restriction in the usual patients with congestive failure is unimportant. However, in the late stages of the disease and in refractory failure this is not so. Apparently, there is a marked increase in antidiuretic hor-

congestion and transudation of fluid into the alveoli The basic mechanisms for its production are similar to those previously discussed

Orthopnea

Patients with pulmonary congestion breathe generally more easily in the upright position. There are several reasons for this. (1) The pulmonary lung volume and vital capacity are increased on assuming the upright position, probably due to the drop in abdominal viscera (2) The work of breathing is decreased in the upright position (3) Upright position promotes a redistribution of fluid allowing edema to go into the lower extremities and abdomen, thus reducing the intravascular blood volume and diminishing pulmonary congestion. In addition, it is possible that in the upright position pulmonary edema tends to accumulate in the bases of the lungs rather than to have a general distribution over the entire lungs In patients with left ventricular failure, orthopnea represents a more advanced degree of pulmonary vascular congestion than does paroxysmal nocturnal dyspnea Chapter 4 presents a more detailed discussion of these clinical features of left heart failure.

Edema

Although many factors involved in edema formation have been explored, the exact mechanisms and sequence of events which result in edema formation in chronic congestive failure are at present unknown One of the most important unsolved questions in development of edema is the nature of the trigger mechanisms which lead to the expansion of the extracellular and intravascular fluid compartments. It is now generally accepted and conclusively shown that *there is* an expansion of the extracellular and intravascular fluid compartments including the total red cell mass in patients with chronic congestive failure [8] The degree to which these are increased depends on the severity of the congestive failure and the amount of edema fluid present Patients with only shortness of breath may have very little increase in intravascular blood volume, whereas patients with ascites, pedal edema and enlarged hearts may have moderate to marked expansion of the intravascular fluid compartments. Nevertheless, it does appear that in order for edema to develop, these fluid compartments must be enlarged. Enlargement of these compartments apparently is produced by the following sequence of events: (a) Sodium is retained, which produces a transient increase in osmolality. (b) This in turn activates the osmoreceptors, and these (c) promote the tubular reabsorption of water in order to re-establish normal osmolality. In addition, water is passively reabsorbed when the glomerular filtration rate is sufficiently decreased [2] This mechanism may be more important than the effect on the osmolar receptor center. Thus, the crucial event in edema formation and the expansion of the intravascular and extravascular fluid compartments is sodium retention These sequences of events may be initiated through the action of the volume receptor center Although it is still uncertain where the volume center or centers are located, there is little doubt as to the existence of some mechanism which regulates intravascular blood volume The adjustments are probably effected by a delicate regulation of tubular reabsorption of sodium In congestive failure there is a shift of blood volume centrally with a relative decrease in volume peripherally It is possible that this is one of the mechanisms by which the chain of events is initiated in the expansion of the intravascular blood volume Other factors which contribute to sodium retention are as follows·

Decreased cardiac output, decreased glomerular filtration rate and tubular reabsorption of sodium The proponents of the "forward" failure theory have postulated that the decrease in cardiac output results in a decrease in renal blood flow and glomerular filtration rate; therefore, a smaller filtered load is presented to the tubules which results in more complete tubular reabsorption of sodium [13, 23] This is one mechanism by which increased sodium is reabsorbed by the tubules However, this is not the only mechanism, since clinical instances have been encountered in which the glomerular filtration rate was reduced below that often seen in congestive failure in the absence of edema (e g., malignant hypertension). In addition, edema

causes toxicity are variable. There are no known drugs which have an established increase in the toxic-therapeutic ratio There are two types of patients in whom toxicity seems clinically to occur more commonly: (1) the patient with cor pulmonale, secondary to advanced, chronic lung disease, such as pulmonary emphysema and (2) the patients with severe functional Class IV long-standing congestive heart failure with very large hearts. The problem of digitalis therapy in these two groups of patients becomes difficult, and these patients often may develop toxic signs and symptoms on relatively small doses of digitalis.

Diuretics

The usefulness of diuretics in patients with congestive failure is well appreciated The chlorothiazide drugs have proved especially helpful in their management As potassium depletion may occur with their use, all patients on chlorothiazide probably should be given supplementary potassium if there are no contraindications Parenteral mercurial preparations are still useful in diuretic therapy

Sodium Restriction

The clinical value of sodium restriction is well recognized, but some patients require severe sodium restriction in order to achieve compensation (200 mg sodium diet) This low sodium diet in itself may promote the development of the hyponatremic syndrome and the physician must be aware of this possibility especially when using severe sodium restriction in the presence of diuretic therapy

Water Restriction

Most patients with congestive heart failure have water retention which responds passively to the tubular reabsorption of sodium In these patients, an increase in sodium output by diuretic therapy or a reduction in sodium intake usually makes the restriction of water unnecessary Thus, patients usually can adjust their own intake of water and fluids ad lib satisfactorily However, in the late stages of congestive failure and in those patients with refractory failure there may occur an increase in an antidiuretic-like substance with the primary retention of water and the subsequent development of the hyponatremic syndrome. In these patients, the treatment of choice is not the addition of hypertonic saline but the restriction of fluid intake during this crucial period

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mone-like substances, causing a primary water retention. This leads to hemodilution, decrease in osmolality of the serum In this late stage of the disease the receptor center apparently fails to function, so that normal osmolality cannot be maintained This is a significant cause of the dilution phenomena and the hyponatremic syndrome which occurs in the course of chronic congestive failure In these instances, it should be emphasized that the proper therapeutic regimen is rigid restriction of fluids rather than the administration of hypertonic saline

Although there are many factors which are known to contribute to sodium reabsorption and the expansion of the extracellular and intravascular fluid compartments, the relative importance of the various factors is not known

Functional Classification

The main difficulty of patients with congestive failure is their inability to carry on a sustained effort without symptoms Thus, the classification of the disease presented by the American Heart Association is a functional one. In general, Class I includes patients with heart disease but without symptoms Class II includes those with shortness of breath or other symptoms only on exertion Class IV represents patients who are completely incapacitated and bedridden; and Class III, those with symptoms between Class II and Class IV However, symptoms also depend on the type of heart disease present. For example, a patient with mitral stenosis may have severe dyspnea, even at rest, due only to the obstruction at the mitral orifice The patient actually may be confined to bed, but without evidence of myocardial failure (no increase in venous pressure, no increase in circulation time, no pedal edema or other evidences of right-sided congestive failure) Often, in such a patient, the development of right ventricular myocardial failure may be associated with a decrease in the severity of the dyspnea. Although in this instance the heart disease has progressed, the functional classification of the patient may improve, changing from Class IV to Class III. Thus, in the functional classification of heart disease, it is important to determine whether the difficulty is due to myocardial or mechanical trouble. Nevertheless, if these factors are kept in mind, the functional classification of patients with congestive failure is easy to accomplish and clinically is quite useful

Therapeutic Principles

It is not within the scope of this discussion to detail the therapy of congestive failure, but certain principles related to the physiology will be presented

Digitalis

Digitalis is still one of the most valuable drugs, if not the most important, in the treatment of congestive failure, and the improper use of digitalis preparations is one of the most frequently encountered defects in the management of the syndrome Frequently, patients supposed to be in refractory failure respond clinically quite well to adequate digitalization achieved by increasing the dosage of digitalis It should be emphasized that the status of the digitalization cannot be evaluated clinically except by the response of the patient, and many patients require an increased dose of digitalis periodically in order to insure adequate digitalis therapy This is necessary in the group of patients who cannot maintain compensation by the usual therapeutic regimens Patients with minimal congestive failure usually have no dramatic response Therefore, the effect also depends on the severity of the congestive failure It should be pointed out that all patients with all types of heart disease may respond to digitalis therapy. It is commonly stated that heart diseases such as thyrotoxicosis, constrictive pericarditis and myocarditis do not respond to digitalis therapy. This is only relatively true in that the response appears to be less than is usually noted; however, instances are repeatedly encountered in which digitalis is effective in these types of heart disease The response of the patient to digitalis gives no clue to the etiology of the heart disease. The problem of digitalis toxicity frequently arises, and the physician must be constantly aware of this possible complication The sensitivity of various patients to digitalis therapy and the amount of the drug which

Physiologic Aspects of Cardiovascular Surgery

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SIGNIFICANT progress in any field of human endeavor is not an isolated phenomenon but rather is the result of many forces working simultaneously in more or less parallel directions. The remarkable achievements of cardiac surgery in the past two decades are the fruition of advances in all the basic medical sciences as well as the clinical fields. The widening sphere of surgical interest in cardiovascular diseases has stimulated an immediate practical application of many basic principles of cardiovascular physiology and, in turn, has demanded a more thorough understanding and investigation of these physiologic concepts.

The cardiovascular surgeon must have his foundation not only in surgical dexterity and technic but also in cardiovascular physiology and hemodynamics. He must put into daily application his knowledge of the physiologic principles that are thus far understood. Many decisions may be made with the advice and consultation of his medical cardiologic colleagues and cardiac physiologists, but no one is better qualified for final judgment regarding such factors as selection of patients for operation, technic of operation and postoperative care than is the cardiac surgeon who also has a broad understanding of the basic principles of cardiovascular physiology.

The interior of the heart remained aloof from the direct inspection and manipulation of the surgeon until it became possible to provide the circulatory needs of the body other than by the action of the heart itself. Although cooling of the body was a temporary solution, relatively unlimited access to the interior of the heart awaited the accomplishment of safe, whole-body perfusion So extensively does this bold enterprise involve not only cardiovascular physiology but the physiology of every organ system of the body that it is of the most pressing importance for the experimental and clinical surgeon to become intimately acquainted with such varied subjects as acid-base balance, solubility of gases in blood, oxygen tension in tissues, pressure, flow, resistance and myocardial physiology.

A classification of diseases of the heart that is oriented toward the physiologic aspects of cardiovascular surgery comprises two primary categories The first includes all types of cardiac lesions in which the disturbed physiology results from an abnormal communication between the pulmonary and systemic circulations. All the remaining cardiac diseases are grouped into a broad classification of mechanical disorders, which includes obstructive lesions, valvular insufficiences and abnormalities limiting the function of cardiac muscle. A combination of these two types of lesions may be present in the same patient.

Abnormal Communications Between Pulmonary and Systemic Circulations

Most lesions of this type are of congenital origin and result from defective partitioning during embryonic development of the original single-chambered heart and circulatory system However, communications between the two vascular systems may be acquired, as in traumatic ventricular septal defects or rupture of an aortic aneurysm into the pulmonary artery.

These communications may be either proximal or distal to the atrioventricular valves. In a physiologic orientation, the former may be considered to be venous communications between the pulmonary and systemic circulations, whereas the latter are thought of as

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Physiologic Aspects of Cardiovascular Surgery

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SIGNIFICANT progress in any field of human endeavor is not an isolated phenomenon but rather is the result of many forces working simultaneously in more or less parallel directions. The remarkable achievements of cardiac surgery in the past two decades are the fruition of advances in all the basic medical sciences as well as the clinical fields. The widening sphere of surgical interest in cardiovascular diseases has stimulated an immediate practical application of many basic principles of cardiovascular physiology and, in turn, has demanded a more thorough understanding and investigation of these physiologic concepts.

The cardiovascular surgeon must have his foundation not only in surgical dexterity and technic but also in cardiovascular physiology and hemodynamics. He must put into daily application his knowledge of the physiologic principles that are thus far understood. Many decisions may be made with the advice and consultation of his medical cardiologic colleagues and cardiac physiologists, but no one is better qualified for final judgment regarding such factors as selection of patients for operation, technic of operation and postoperative care than is the cardiac surgeon who also has a broad understanding of the basic principles of cardiovascular physiology.

The interior of the heart remained aloof from the direct inspection and manipulation of the surgeon until it became possible to provide the circulatory needs of the body other than by the action of the heart itself. Although cooling of the body was a temporary solution, relatively unlimited access to the interior of the heart awaited the accomplishment of safe, whole-body perfusion. So extensively does this bold enterprise involve not only cardiovascular physiology but the physiology of every organ system of the body that it is of the most pressing importance for the experimental and clinical surgeon to become intimately acquainted with such varied subjects as acid-base balance, solubility of gases in blood, oxygen tension in tissues, pressure, flow, resistance and myocardial physiology.

A classification of diseases of the heart that is oriented toward the physiologic aspects of cardiovascular surgery comprises two primary categories. The first includes all types of cardiac lesions in which the disturbed physiology results from an abnormal communication between the pulmonary and systemic circulations. All the remaining cardiac diseases are grouped into a broad classification of mechanical disorders, which includes obstructive lesions, valvular insufficiences and abnormalities limiting the function of cardiac muscle. A combination of these two types of lesions may be present in the same patient.

Abnormal Communications Between Pulmonary and Systemic Circulations

Most lesions of this type are of congenital origin and result from defective partitioning during embryonic development of the original single-chambered heart and circulatory system. However, communications between the two vascular systems may be acquired, as in traumatic ventricular septal defects or rupture of an aortic aneurysm into the pulmonary artery.

These communications may be either proximal or distal to the atrioventricular valves. In a physiologic orientation, the former may be considered to be venous communications between the pulmonary and systemic circula-

arterial communications These two types of communications produce entirely different hemodynamic alterations, which result in different natural progression of cardiac disability. Combinations of these defects exist in which the communication may be between a chamber distal to the atrioventricular valves and one proximal to them, such as an aneurysm of the aortic sinus that has ruptured into the right atrium, or a ventricular septal defect emptying into the right atrium

Venous Intercirculatory Communications

The commonest example of this type of lesion is the atrial septal defect, which may be combined with various degrees of anomalous connection of the pulmonary veins Since the pressure relationships between the pulmonary and systemic venous chambers, including the atria, are normally not drastically different, it is of interest and much importance to inquire into the reasons for the direction and magnitude of any shunt across an atrial septal defect.

What are the determinants of the right and left atrial pressures in the normal heart, and what determines the shunt occurring through an atrial septal defect if the pressures in the two atria under this circumstance are nearly equal? Since the venous side of the circulation is largely passive and is predominantly controlled by ventricular action, the clue to the answer to these questions is found in the characteristics of the ventricles into which each of the respective venous chambers empties. The left ventricle is a thick-walled, muscle-bound structure whose chief function is to pump blood under relatively great pressure. On the other hand, the right ventricle is more thin-walled and can pump large volumes of blood under low pressure against the low pulmonary vascular resistance.

In the presence of a large atrial septal defect, the atrial chambers functionally become a single chamber with a single head of pressure that empties into the two ventricles during diastole. The volume of blood that each ventricle accepts under these conditions, relative to the opposite ventricle, determines the volume and direction of the shunt through the septal defect. Before the development of increasing vascular resistance, the right ventricle is much more distensible and can accept four or more times as much blood during each diastole as can the thick-walled and less distensible left ventricle Consequently, it accepts not only all the blood entering the right atrium from the venae cavae but also a large proportion of the blood entering the left atrium from the pulmonary veins. Under such conditions, surgical closure of the defect would result in the prompt return of cardiac function and pressure relationships to normal. Such an operation is extremely well tolerated by the patient

Any technic of closure of the defect that results in its complete and permanent obliteration has proved to be a safe and successful procedure in these patients Consequently, the semi-open, atrial well technic or the open technics of repair with the aid of hypothermia or extracorporeal circulation have given generally excellent results An operative mortality rate of less than 2 per cent in this group of uncomplicated lesions is attainable

The presence of one of the various types of partial anomalous pulmonary venous connection associated with an atrial septal defect modifies in relatively minor ways the hemodynamic effect of the atrial septal defect, but such anomalous veins may present increasingly complicated technical problems during repair. Prolonged exposure at operation may be necessary, so that the ideal surgical approach is that provided by extracorporeal circulation This is particularly true in the various forms of total anomalous pulmonary venous connection Again, in the absence of severe pulmonary vascular changes, rerouting of the venous return to the normal respective atria and ventricles results in immediate relief of the hemodynamic derangement that these lesions impose; therefore, such an operation is relatively well tolerated by the patient.

Up to this point, this discussion has been limited to hemodynamically uncomplicated abnormal communications between the venous sides of the pulmonary and systemic circulations. The chief complicating feature that may occur in these patients is the development of

pulmonary vascular obstruction, which is associated in some way with the greatly increased pulmonary blood flow. Through the years, pulmonary vascular obstructive changes may progress, and the pulmonary vascular resistance may reach such a high point that a severe burden is imposed on the heart, particularly the right ventricle. This rarely occurs early in life; ordinarily, its onset is delayed until the third and sometimes until even the seventh decade of life. The rate of appearance of these pulmonary vascular changes is subject to wide variation from patient to patient but, in general, they develop much less rapidly in patients with abnormal connections between the venous sides of the two circulations than they do in patients whose connections are between the arterial sides.

The formula for flow, flow equals pressure divided by resistance ($F = P/R$), is fundamental to an understanding of the hemodynamic alterations resulting from progressive pulmonary vascular obstruction. From this principle, it can be adduced readily that, as these pulmonary vessels become narrowed, one of two things, or both, must occur. If pulmonary blood flow remains constant, the pressure in the pulmonary arterial system must increase. Such a situation pertains in the early stages of pulmonary hypertension and continues as long as the right ventricle is able to pump an excessive volume of blood at *the increased pressure* required. As a result of this *increasing* load, the right ventricle becomes progressively more hypertrophied and may approximate the left ventricle in the thickness of its muscular wall, thus acquiring characteristics of distensibility similar to those of the left ventricle. Because of this, the right ventricle is able to accept less and less blood from the functionally single atrium so that the *pulmonary blood* flow progressively diminishes. It is uncommon, however, for the right ventricle of a patient having a venous intercirculatory communication not to maintain a pulmonary blood flow that is greater than the *systemic flow*.

In theory, any patient having an abnormal communication between the pulmonary and the systemic circulation, whether venous or arterial, should benefit by closure of that abnormal communication as long as the predominant flow of blood through the defect results in a pulmonary blood flow larger than the systemic flow; if that is true, closure of the communication would result in a lower pressure within the pulmonary arterial tree and would relieve much of the increased work of the heart.

In practice, however, all patients with a venous intercirculatory communication who have a pulmonary blood flow greater than the systemic flow are not necessarily safe candidates for operation. For example, whenever pulmonary vascular resistance causes pulmonary blood flow to diminish until it is only 10 or 20 per cent greater than the systemic flow, a profound disturbance in the work potential of the right ventricle must have occurred. This might, for the sake of convenience, be referred to as "failure" of the right ventricle. With such failure, and hence with pulmonary blood flow not greatly increased above systemic flow, the burden of the failing right ventricle is not dramatically relieved by repair of the venous intercirculatory communication. In such a situation, the presence of tricuspid insufficiency must be sought and, if found, corrected, since such correction would reduce the load on the right ventricle and facilitate postoperative recovery.

Analysis of accumulated experience with the repair of atrial septal defects in adults has revealed several factors determinable preoperatively that appear to have a strong influence on the operative risk. Of these factors, *a greatly increased pulmonary vascular resistance* with its associated severe pulmonary hypertension, failure of the right ventricle with its typical clinical characteristics and greatly increased right atrial pressure, and a large right-to-left shunt* are significantly related to survival of the patient after operation.[12]

Occasionally, it may be noted that a patient who has an atrial septal defect will show evi-

* The arbitrary values given these pronouncedly abnormal parameters are: peak right atrial pressure greater than 15 mm. Hg, right-to-left shunt greater than 10 per cent of systemic blood flow, systolic pulmonary or right ventricular pressure greater than 75 mm. Hg and a ratio of pulmonary to systemic vascular resistance *greater than 0.5*.

dence of failure of the right side of the heart, yet the pulmonary hypertension is not severe and the pulmonary vascular resistance is not greatly increased The commonest cause of this situation is a significantly malfunctioning atrioventricular valve, either mitral or tricuspid, which causes an increased pressure in the functionally common atrium.

Arterial Intercirculatory Communications

All abnormal communications between the pulmonary and systemic circulations distal to the atrioventricular valves are included in this category Ventricular septal defect, truncus arteriosus, aorticopulmonary window and patent ductus arteriosus are classic examples. Hemodynamically, these lesions show similarities, and the considerations leading to selection of patients with such lesions for operation are related

The direction and the magnitude of the shunt through an arterial intercirculatory communication are related directly not only to the size of the defect but also to the relative vascular resistances of the two arterial systems. Initially, before the development of pulmonary vascular obstructive changes, the resistance to the flow of blood through the pulmonary circulation is much less than it is to flow through the systemic circulation, consequently, when the defect is large, an immense shunting of blood from the systemic to the pulmonary system occurs. This large volume of shunted blood is pumped by the left ventricle and imposes a tremendous overload on that chamber, resulting in left ventricular enlargement and often failure. Therefore, infants and children are prone to the development of recurrent bouts of heart failure, pulmonary edema and pneumonia.

As is true of venous intercirculatory communications, arterial intercirculatory communications also show progressive development of obstructive changes in the peripheral pulmonary vasculature.[6] When the communication is large in relationship to the cross sectional diameter of the aorta, these pulmonary vascular changes usually appear earlier in life than is true of patients having a venous intercirculatory communication. Thus, severe pulmonary hypertension is common even in the first decade of life in patients who have, e g, a ventricular septal defect, in contrast to its late appearance in those patients having an atrial septal defect.

As the pulmonary vascular resistance increases in the presence of an arterial intercirculatory communication, the pressure in the pulmonary artery gradually increases until finally it may equal the systemic arterial blood pressure. When this occurs, further increase in pulmonary vascular resistance must lead to progressive diminution in pulmonary blood flow As the latter diminishes toward equality with systemic blood flow, the volume of blood that must be pumped by the left ventricle also progressively diminishes, consequently, that chamber may return gradually toward normal size The peripheral lung fields, as seen on the thoracic roentgenogram, then may no longer show evidence of engorgement, and the electrocardiogram may indicate progressive diminution in overwork of the left ventricle. Coincident with this relief in the burden of the left ventricle, the clinical status of the patient may appear to improve and his general vitality increase This patient, who is approaching inoperability, since his pulmonary blood flow is diminishing toward equality with the systemic flow, is, therefore, symptomatically rather well, in sharp contrast to the patient approaching inoperability who has a venous intercirculatory communication

With still further increase in pulmonary vascular resistance, pulmonary blood flow becomes less than systemic flow, the predominant shunt through the communication is then from right to left and cyanosis appears; later, progressive failure of the right side of the heart may develop Such a condition in the presence of a ventricular septal defect might be referred to by some as Eisenmenger's syndrome; in the case of a patent ductus arteriosus, it is often called a "reversing ductus " These patients are considered inoperable in the sense that closure of the defect would only serve to increase the right ventricular and pulmonary arterial pressures and thus increase the burden on the right ventricle.[3]

The technic of repair of arterial intercircu-

latory communications is not a controversial issue. The patent ductus arteriosus may be closed without the need for complicated procedures, although, in the case of a hypertensive ductus, the use of trimethaphan (Arfonad) camphorsulfonate or a similar agent to produce hypotension at operation has given considerable technical benefit.[8] An aorticopulmonary window can be repaired without the use of extracorporeal circulation, but the latter technic is preferred, since it gives the best control against surgical hemorrhage and greatly facilitates the technical aspects of closing of the window

A ventricular septal defect can be repaired satisfactorily at this time only with the use of extracorporeal circulation, the physiologic principles of which are to be discussed later. Whether a ventricular septal defect is closed by direct suture or by the insertion of a prosthesis appears relatively unimportant from a functional standpoint Of considerable importance is whether or not complete heart block is present after repair. This complication imposes severe physiologic disturbances because of the resulting slow cardiac rate and the ever present threat of complete cardiac asystole. It has been demonstrated in animals[16] *that the* stroke volume of the acutely blocked heart cannot be increased beyond a certain maximum, thus, when the cardiac rate decreases below approximately 90 beats per minute, cardiac output likewise must diminish In the postoperative patient, cardiac output is curtailed as the result of complete heart block until the heart has time to dilate and thus to compensate for the slower rate by a larger stroke volume Consequently, during the postoperative period, when there may be an in-

[illegible] during the first several postoperative days to maintain all patients who have complete heart block by means of an electric pacemaker[17] adjusted to establish a cardiac rate of about 100 beats per minute

Other technical factors in closing a ventricular septal defect may play an important role in the cardiocirculatory function after operation. The length of the incision for ventriculotomy bears a relationship to the work capacity of the right ventricle after its closure,[16] for the longer the incision, the greater is the number of divided myocardial fibers and hence the weaker is the ventricular contraction When prolonged (20 to 30 minutes) cardiac asystole, or cardioplegia, is induced, a price must be paid in terms of the reduced myocardial work capacity,[13] although this price is considered by many surgeons to be sufficiently cheap to warrant its continued use Whether or not asystole is induced by injection of chemicals into the coronary circulation or by the interruption of coronary circulation alone appears to be of little importance. Repeated interruption of coronary blood flow for intervals of about five minutes appears to have no deleterious myocardial effects, and clinical experience has indicated that ischemic asystole may be maintained safely in the nonfailing heart for 20 to 30 minutes if necessary. Periods of cessation of coronary flow up to 60 minutes with survival have occurred.[13]

Mechanical Cardiovascular Lesions

This broad designation includes any abnormality of cardiovascular function that is the result of some deformity in any portion of the cardiovascular system causing mechanical insufficiency. From the standpoint of function, these deformities can be classified into three categories, namely (1) various obstructive cardiovascular lesions, (2) cardiac valvular insufficiency and (3) mechanical abnormalities that interfere with the function of the myocardium itself.

Obstructive Lesions

This category includes all lesions that abnormally narrow the pathway of blood flow, such as stenosis of any of the cardiac valves, the ventricular outflow tracts, or the pulmonary artery or aorta above its valve The various forms of coarctation are also typical. When the obstruction is significant and is not circumvented by collateral circulation, there is always an increase of pressure proximal to the stenosis, with a pressure gradient across the zone of obstruction.

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during systole in a reverse direction into the atrium; if the exit valve is incompetent, a portion of the blood that is ejected into the respective artery during systole returns to the ventricle during the following diastole. The hypertrophied ventricle responds to the increased

Valvular insufficiency is a mechanical aberration that should be ideally amenable to surgical correction. Although successful repair has been accomplished by open-heart operations for mitral and aortic valvular lesions of this type, the technical ability to restore consistently satisfactory and permanent valvular competence is still lacking. Prosthetic devices for safe total replacement of severely and irreparably destroyed valves have not yet been developed, although many investigators are working on this problem The three chief obstacles to the quest for a prosthetic valve are related to the design and construction of a mechanically favorable valve, fixation of the valve in the correct position within the heart, and avoidance of propagation of the thrombus and embolization

By the technics for repair of mitral and tricuspid valves now employed, including annuloplasty, valvuloplasty and replacement of valvular leaflets by a nonmoving rigid prosthetic "shoulder," much palliation can be accomplished in many patients. All symptoms of cardiac disease can be eliminated, hemodynamics may be restored to normal (Fig. 1) and the size of the heart may regress toward normal.

Similarly, excellent improvement may be given the patient who has aortic insufficiency if his disease is amenable to the available technics, such as suture of torn cusps, excision of the noncoronary valve cusp and "bicuspidization" of the aortic valve, structural restoration of the valvular cusp by means of reinforcing prosthetic cloth and resupport and shortening of displaced and herniating cusps. In anticipation that valvular lesions favorable for repair will be encountered, operation even in the present state of technical inadequacy is indicated for patients who have severe aortic insufficiency.

Abnormalities Limiting Function of Cardiac Muscle

In this physiologic orientation, there remains a group of conditions in which valvular function is normal and the pathways for blood flow are unobstructed but the heart performs an inadequate amount of effective work to maintain its proper output. A miscellaneous group of lesions may cause this, including the closely related conditions of constrictive pericarditis, cardiac tamponade and endocardial fibroelastosis A ventricular aneurysm, because of its paradoxical motion, also may effectively in-

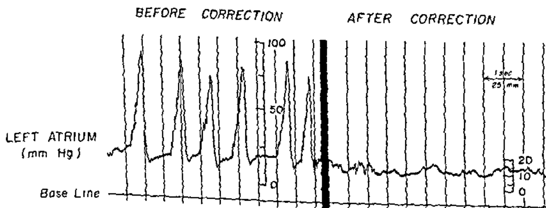


Fig 1 —Left atrial pressure before and after mitral valvuloplasty in a 53 year old laborer The mitral insufficiency was on the basis of a ruptured chorda tendinea. The patient resumed full employment (Reproduced with the kind permission of the publishers from McGoon, D C Repair of mitral insufficiency due to ruptured chordae tendineae J. Thoracic Surg 39 357-362 [Mar] 1960)

In coarctation, the physiologic explanation for the increased pressure proximal to the lesion has been the subject of considerable study and argument[1,4] The simplest explanation is that the coarctate segment and collateral channels impose resistance to blood flow and, therefore, a greater pressure is required to maintain normal blood flow to the body peripheral to the coarctation However, the mean pressure in the vessels below the coarctation may be greater than normal rather than less Also, after surgical relief of the coarctation, the blood pressure in the arms usually remains increased for a few days and then only gradually declines, although the obstruction is totally relieved by operation For these and other reasons, it has been postulated that a renal pressor mechanism may play an important etiologic role in the hypertension of coarctation

When an obstructive lesion such as mitral stenosis increases the pulmonary venous pressure, an associated increase in pulmonary arterial resistance may occur This gradual development of pulmonary arteriolar narrowing apparently has the beneficial effect of protecting the lungs from the hazard of pulmonary edema However, after relief of the pulmonary venous hypertension, as by mitral commissurotomy, the increased pulmonary vascular resistance may not decline quickly but may delay the anticipated amelioration of pulmonary hypertension

For any centrally located obstructive lesion, it is clear that surgical intervention is accomplished most safely and satisfactorily early in the course of the disease, before the tissues proximal to the obstruction undergo severe alterations Adverse alterations caused by the various obstructions include myocardial changes from long-standing ventricular failure, massive atrial dilatation, severe pulmonary vascular obstructive changes and chronic passive congestion of various viscera. However, for the proper timing of surgical intervention, careful consideration must be given to the hazards involved in the operation, the rapidity with which the disease is advancing in that patient and the degree of perfection that can be expected of the operation to correct the obstructive deformity. For patients in whom operation is relatively safe and successful, surgical correction is recommended either before the onset of symptoms, such as in coarctation, or when it becomes evident that symptoms are appearing and are progressive, such as in mitral stenosis and acquired aortic stenosis, or when signs indicate that a significantly severe stenosis is present and symptoms may be expected in the near future, such as in congenital pulmonary or aortic stenosis Technical advances ultimately should make all obstructive lesions treatable by early corrective operation.

If pulmonary valvular stenosis has resulted in obstructive muscular hypertrophy of the outflow tract of the right ventricle, some uncertainty remains as to how radically this secondary obstruction must be treated at the time of operation In this situation, the gradient across the outflow tract of the right ventricle and pulmonary valve usually cannot be relieved simply by widely opening the pulmonary valve itself Such muscular hypertrophy of the outflow tract must be excised at the time of pulmonary valvulotomy in order to relieve the pulmonary stenosis as nearly completely as is possible, and this should best assure a smooth postoperative recovery for the patient. On the other hand, it has been demonstrated in at least some patients of this type that the muscular hypertrophy has regressed during the months following pulmonary valvulotomy, and the pulmonary gradient remaining in the immediate postoperative period has disappeared correspondingly This important point cannot be settled conclusively until more information is known as to how consistently residual infundibular hypertrophy and stenosis can be expected to disappear spontaneously after relief of the pulmonary valvular stenosis

Valvular Insufficiency

Valvular insufficiency, or incompetence, reduces cardiac efficiency The ventricle that is handicapped by significant valvular insufficiency must pump a greatly increased volume of blood to maintain its normal output, since not all of the blood that it receives during each diastole contributes to the effective cardiac output. When the atrioventricular valve is incompetent, a portion of the blood is ejected

during systole in a reverse direction into the atrium, if the exit valve is incompetent, a portion of the blood that is ejected into the respective artery during systole returns to the ventricle during the following diastole. The handicapped ventricle responds to the increased volume load placed on it by undergoing hypertrophy and dilatation.

Valvular insufficiency is a mechanical aberration that should be ideally amenable to surgical correction. Although successful repair has been accomplished by open-heart operations for mitral and aortic valvular lesions of this type, the technical ability to restore consistently satisfactory and permanent valvular competence is still lacking. Prosthetic devices for safe total replacement of severely and irreparably destroyed valves have not yet been developed, although many investigators are working on this problem. The three chief obstacles to the quest for a prosthetic valve are related to the design and construction of a mechanically favorable valve, fixation of the valve in the correct position within the heart, and avoidance of propagation of the thrombus and embolization.

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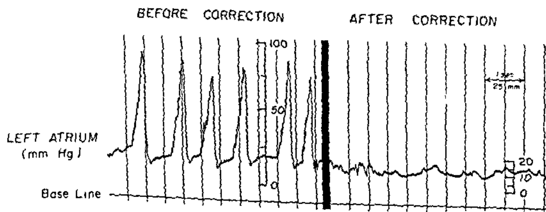


Fig. 1.—Left ...

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hibit satisfactory ventricular output Myocardial ischemia, as from coronary atherosclerosis, may have a similar result Some of these lesions are obviously correctable by operation, but, particularly in coronary arterial disease, the obstacles to effective surgical treatment have not yet been surmounted

Combinations of Mechanical Disorders and Intercirculatory Communications

As a result of more extensive dysgenesis, certain forms of congenital heart disease may involve not only intercirculatory communications but also mechanical disorders. The physiologic disturbances associated with these conditions are often profound Most patients who have cyanotic heart disease fit into this category, since an intercirculatory communication must be present to enable the right-to-left shunt of blood that results in cyanosis, and since an obstructive lesion such as pulmonary stenosis is usually present that shunts blood from right to left through the septal defect This group of lesions also includes the endocardial cushion defects in which septal defects are combined with deformity and incompetence of one or both of the atrioventricular valves

The tetralogy of Fallot is of particular interest from the physiologic standpoint Its two essential features are a ventricular septal defect of a size approximating that of the aortic valvular orifice and pulmonary stenosis of a degree sufficient to cause equality of pressures in the two ventricles Closely related deformities may occur, as an extremely small ventricular septal defect associated with pulmonary stenosis, or mild pulmonary stenosis associated with an otherwise typical ventricular septal defect

When cyanosis results from the tetralogy of Fallot, the total blood flow through the heart is decreased because of diminished pulmonary blood flow. Consequently, the work of the heart is not excessive, and the cardiac size remains within normal limits The right ventricle must eject its blood against systemic arterial pressure, and it responds to this increased pressure load by hypertrophy of its walls Since it is not called on to pump a volume of blood greater than the systemic blood flow, the right ventricle is able to cope satisfactorily with its burden of pressure The left ventricle needs to propel only the diminished volume of blood returning from the lungs, and hence its work capacity is not increased

To be successful, direct repair of this complex deformity must result in as normal a hemodynamic state as possible,[9] for partial repair of the ventricular septal defect or pulmonary stenosis has proved to be poorly tolerated The heart in the tetralogy of Fallot is little prepared for the increased work load that would be imposed by the presence of a residual ventricular septal defect and its consequent left-to-right shunt When severe pulmonary stenosis is permitted to remain after tight closure of the ventricular septal defect, acute or subacute failure of the right side of the heart must be expected It is this stringent requirement for precise repair plus the lack of latitude for technical error that may be reflected in the unsatisfactory results of open-heart repair of the tetralogy of Fallot in the initial experience of most surgical teams.

For the same reasons, the less satisfactory but also less dangerous palliative surgical technics for the repair of this lesion, such as the Blalock or the Potts operation, are still being employed in many surgical centers, and they may continue for some time to be the method of choice for treatment in certain selected cases of this condition that least lend themselves to satisfactory direct repair This is true particularly of the small, deeply cyanotic, desperately incapacitated child.

It is also essential in endocardial cushion lesions that precise repair of the valvular deformity be done in addition to closure of the septal defects. Thus, in partial atrioventricular canal, simple closure of the ostium primum atrial septal defect without relief of mitral insufficiency probably would lead to greatly increased left atrial pressure, pulmonary edema and increased postoperative mortality rates.

Requisites for Open-Heart Operations

Open operations on the nonfunctioning heart are currently possible through the employment

of either of two methods. The absolute dependence of tissues on the continuous circulation of blood can be altered temporarily by reducing the temperature of the tissues (body hypothermia), or circulation of blood through the body may be accomplished by artificial means (extracorporeal circulation) in temporary substitution for the function of the heart.

Hypothermia

Sufficient calories can be extracted from the relaxed body by a variety of means to decrease its temperature to a desired level. As the temperature of the tissues diminishes, the need for oxygen and nutritive elements progressively declines, so that increasingly long intervals without circulation of blood can be tolerated. The central nervous system is the most critical structure of the body in this regard, and it can tolerate the absence of blood flow for the least time Relatively mild body hypothermia, such as 32 C , permits cessation of circulation to the brain for a period of at least six minutes without producing irreversible cerebral changes Relatively few cardiac defects can be corrected in so short a time, yet efforts to prolong this interval by use of more profound hypothermia have been hampered by the problem of ventricular fibrillation, which is likely to develop at these decreasing temperatures. This problem has been overcome by combining the use of whole-body perfusion with deep hypothermia to replace the function of the heart and lungs during cooling and warming processes

Combined Profound Hypothermia and Extracorporeal Circulation

This technic not only avoids the problem of ventricular fibrillation, in that the circulation is maintained by the extracorporeal circuit even if ventricular fibrillation develops, but also provides a ready means of extracting calories from the body by the use of a heat exchanger incorporated in the extracorporeal circuit Since the incision into the heart need not be made before cooling is completed and all circulation through the body discontinued, it has been found that the patient's own lungs may be satisfactorily employed to provide exchange of gases for the blood during the cooling and rewarming periods.[8]

Both in its experimental and clinical application, profound hypothermia has permitted prolonged cessation of circulation to the body with recovery.[8] Certain technical surgical problems that the cardiovascular surgeon encounters, such as complete transposition of the great vessels, could be handled most satisfactorily in the complete absence of circulation of blood through the body. Physiologic disturbances imposed by severe hypothermia might well be acceptable for some operations in view of the technical advantages they provide. These disturbances are under study; as they become better understood, the ultimate role of hypothermia in cardiac surgery will be determined.

Normothermic Whole-Body Perfusion

A tremendous amount of study has been devoted during the past decade to the alterations in body physiology that occur during and after use of whole-body perfusion A stimulus for this study has been the need to determine the optimal system of perfusion that should be employed in surgical practice With increasing experience and knowledge, the opinion now is generally accepted that any clinically employed system of perfusion should closely simulate most features of the normal circulation of blood as it is accomplished by the heart and lungs themselves.[10] The machinery that may accomplish this feat successfully is subject to wide variation

The amount of blood perfused through the body should approximate the normal cardiac output of the anesthetized patient, which amounts to approximately 2.4 L. per minute per square meter of body surface The arterial blood should be normally saturated with oxygen, which, in conjunction with adequate rates of blood flow, assures venous oxygen saturations in the normal range Venous return from the patient to the extracorporeal circuit must be accomplished without significantly increasing the venous pressure, and this is best done in a manner simulating normal venous drainage, namely by using the largest possible venous cannulas and applying steady gentle negative pressure to them.

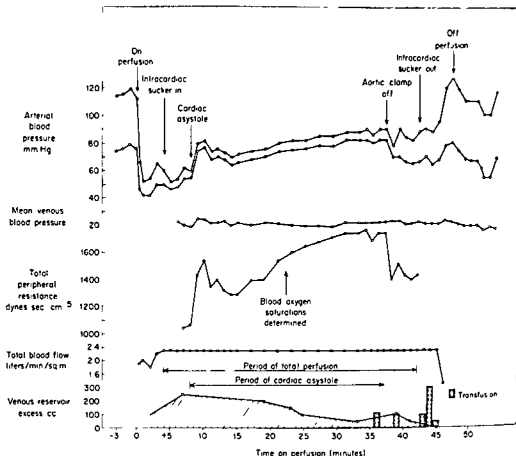


FIG 2 —Hemodynamic status during perfusion employing a system whereby total blood flow is maintained at an optimal rate Note the gradual increase in total peripheral resistance during perfusion, and the stable level of venous pressure The "venous reservoir excess" is the volume of blood withdrawn from the patient's circulation and temporarily sequestrated in the extracorporeal circuit, it is thought to represent the central blood volume of the patient (Reproduced with the kind permission of the publishers and the authors from McGoon and associates [11])

Although a pulsatile arterial pressure is natural, conclusive evidence has not been presented to demonstrate that nonpulsatile flow of a similar volume is less satisfactory, and this has been the chief feature of most systems of perfusion that has not simulated the physiologic norm. With the aforementioned rate of perfusion for the anesthetized patient, the mean arterial blood pressure at the onset of perfusion is subnormal A tendency to a gradual increase in peripheral vascular resistance during perfusion results in a similar gradual increase toward normal of arterial pressure during perfusion[11] (FIG. 2). Since peripheral arterial resistance is subject to wide variation and is influenced by several mechanisms, those systems of perfusion appear faulty which disregard the rate of blood flow but rather perfuse at a rate sufficient to maintain a given blood pressure

The partial pressure of carbon dioxide during extracorporeal heart-lung bypass is largely controllable in most systems of perfusion through alteration in the rate of ventilation of the oxygenator and in the fractional concentration of carbon dioxide in the gas passing through the oxygenator The partial pressure of carbon dioxide in the arterialized blood apparently is best maintained at levels that are less than normal, since this hypocapnia tends to prevent spontaneous respiratory movements by the patient but is probably not sufficiently severe to cause extensive reduction of cerebral blood flow [7]

The development of mild metabolic acidosis

during general anesthesia is usual. Further progression of metabolic acidosis should not occur during perfusion if adequate flow rates of fully oxygenated arterial blood are employed.[14]

Determinations of the consumption of oxygen before and after perfusion have not been done in clinical cases, therefore, control values for comparison with oxygen consumption data during perfusion are not known. Available data may be interpreted as indicating that the oxygen uptake of a patient during perfusion increases with increasing perfusion flow rates only to a certain point, beyond which it remains unchanged with further increases in flow. At this point, the rate of blood flow probably results in perfusion of the entire body rather than limited parts of it. Further increases of flow beyond this point, while not increasing the oxygen uptake, produce a smaller difference in the amount of oxygen in arterial and in venous blood. Oxygen uptake during apparently adequate whole-body perfusion averages about 130 ml per minute per square meter of body surface, which is comparable to the oxygen uptake in anesthetized intact patients Thus, it is concluded that the entire body is perfused by the rate of perfusion already described

Systems of perfusion based on the aforementioned considerations have had extensive clinical trial, and the results indicate a high degree of safety. Under such conditions, cessation of cardiac function can be tolerated for one to two hours without apparent serious physiologic disturbances

Combined Mild Hypothermia and Extracorporeal Circulation

Mild hypothermia may be combined with whole-body perfusion to obtain the theoretic advantage of a lower rate of perfusion[12] This reduction in blood flow during perfusion often enables a more nearly bloodless operative field in which to work, for coronary and bronchial flows likewise are reduced Smaller heart-lung machines, with smaller amounts of priming blood, are thereby permitted, and it is also thought that less trauma to the blood may occur

A Final Word

Many physiologic aspects of cardiovascular surgery are related to the other disciplines covered in this book or are beyond the scope of this chapter For as dynamic a unit as the cardiovascular system, an understanding of its physiologic aspects is equally as important to the successful outcome of the cardiovascular surgeon's efforts as is the dexterity with which such efforts are accomplished.

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Section IV

ASSOCIATED FUNCTIONS OF THE HEART AND LUNGS

The Dynamics of the Normal Pulmonary Circulation

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THE pulmonary circulation is an integral part of the cardiorespiratory system and is influenced directly and indirectly by alterations in the function of other components of this system. In this chapter, attention will be restricted to the dynamics of the circulation through the pulmonary vessels. Consideration of the control of the volume of venous return and of the function of the right heart has been excluded, and likewise, no attempt will be made to discuss the factors influencing left atrial pressure, such as the efficiency of the left ventricle and the state of the mitral valve, although these factors have an important influence on the pulmonary circulation. The pulmonary circulation will be considered under three headings: the structure of the pulmonary vessels, the hemodynamic variables and their measurement, and finally, the regulation of the normal pulmonary circulation.

The Anatomy of the Pulmonary Blood Vessels

Although the gross anatomy of the larger pulmonary vessels has been well described, the arrangement of the small vessels in the lung has received less attention. Some knowledge of the anatomy of these vessels is fundamental to an orderly presentation of the physiology of the normal circulation.

The lung is supplied with blood by both the pulmonary and bronchial arteries. In general, the pulmonary arterial divisions accompany the ramifications of the bronchial tree, so that each bronchiole supplying a secondary lobule is accompanied by a small pulmonary artery. The media of these vessels contain muscle fibers bounded on each side by a layer of elastic tissue. Nerve fibers have been demonstrated within the media of such vessels,[23] but their exact course from the sympathetic and parasympathetic fibers that enter the lung is uncertain.

At the level of the respiratory bronchioles, which radiate from the middle of the secondary lobule, the smallest arteries (about 100 microns in diameter) give rise to arterioles. The walls of the pulmonary arterioles contain only scattered muscle bundles, and their branches, the precapillaries (about 70 microns in diameter), contain none.[39]

The capillaries of the alveolar walls drain through postcapillaries to venules and then to small veins situated in the interlobular septa. In the smallest veins, muscle cells are sparse, but in veins of intermediate size there is a well-developed muscular media that is thicker in relation to the size of the lumen than it is in the large veins.

In normal lungs, the bronchial arteries are relatively small vessels arising from the aorta or its branches. They follow the dividing bronchi into the lung and supply oxygenated blood to all parts of the lungs except the alveolar walls. Small branches are found in the interlobular septa and pleura, and others follow the bronchial tree as far as the respiratory bronchioles where they end in capillaries that anastomose with those arising from the pulmonary arteries. Bronchial veins drain only structures near the hilus. Much of the blood from the bronchial artery having traversed the capillaries flows via short veins which run from the region of the small bronchioles and respiratory bronchioles to the pulmonary venous system. Precapillary anastomoses between the bronchial and pulmonary arteries exist in normal

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lungs but are small and sparse in comparison with those that can be found in pathologic lungs. These anastomoses are found in relation to bronchi and beneath the visceral pleura. Since the bronchial arteries receive autonomic nerve fibers, it has been conjectured that the caliber of these anastomotic channels is under vasomotor influence and hence that their caliber may have some regulatory significance.

The existence of pulmonary arteriovenous anastomoses in the human lung is less certain. As much as 7 per cent of the blood flow through the lungs may not be exposed to normal oxygenation.[7] This is largely due to blood flow through poorly ventilated alveoli, the remainder, the anatomic shunt, is due to blood which has not traversed alveolar capillaries The blood from the thebesian veins and from pulmonary veins draining capillaries supplied by the bronchial arteries falls into this category, but direct pulmonary arteriovenous anastomoses also have been proposed as an alternative source of shunted blood Although such anastomoses have not been demonstrated histologically in lungs, glass spheres up to 500 microns in diameter have been shown to pass through the vascular bed of excised human lungs[38] Other investigators have obtained similar results in living experimental animals, and blood flow through pulmonary arteriole-venule shunts has been observed in the transilluminated lungs of rabbits and guinea pigs.[26] However, more observations are required before the functional significance of such connections in normal human lungs can be assessed

Hemodynamic Parameters and Their Measurement

Advances in the study of the pulmonary circulation in recent years have been based principally on the technic of cardiac catheterization, which was first applied to man by Forssman[17] in 1928 and which has been developed and extended by Cournand and Ranges[10] and many others during the past decade This technic provides access to the chambers of the heart and great vessels; pressures at the tip of the catheter may be measured, samples of blood may be removed or an indicator injected

Intravascular Pressure

In the heart and blood vessels, pressures are measured relative to an arbitrary zero that is established in a constant relation to the heart. In this laboratory, the reference position is half the distance from the top of the table to the sternum with the patient supine, i e., approximately at the level of the right atrium.

The strain-gauge manometer is probably the instrument most commonly used today for measuring pressures[28] This highly reliable instrument has both a linear calibration and a low-volume displacement relative to the change in pressure. Since the ejection of blood from the heart is intermittent, intravascular pressures change in phase with cardiac action. Such pressure pulses in the cardiovascular system exhibit phasic variations of widely differing frequencies In the reproduction of these phenomena, the characteristics of all components of the recording system are important. For practical purposes a catheter-manometer system with a frequency response which is uniform (100 per cent of static) to 20 cps is adequate to record most of the hemodynamically important components of the cardiovascular pressure pulses in man[42] For very fast components, phase lag and some reduction in amplitude may occur with the use of such systems Since most pressures are recorded by means of flexible catheters which are filled with fluid, the motion of the catheter when threaded through the beating heart may generate artifacts which are not representative of the changes in pressure at the catheter tip These artifacts predominantly occur at frequencies in excess of 20 cps, and their effects may be minimized by use of catheter-manometer systems of lower dynamic response. If recordings of intravascular pressure with dynamically important components of faster frequencies are required, either a direct needle puncture of the vessel concerned may be made,[33] or if a catheter must be used, the pressure-sensing unit should be positioned at the catheter tip,[14] in order to avoid artifacts of the type mentioned.

In the pulmonary circulation, the pressures in the pulmonary artery generated by the right ventricle serve to transfer blood through the pulmonary blood vessels into the left atrium

TABLE 1 —*Pulmonary Pressure in Resting Normal Human Beings*

	Main Pulmonary Artery,* mm Hg			Pulmonary Artery Wedge, mm Hg†		
	Systolic	Diastolic	Mean	Maximum	Minimum	Mean
Average values	22	12	17	15	9	12
S D ‡	3 7	2 6	3 1	2 9	2 2	2 0
Extreme values						
upper	28	16	22	20	13	15
lower	13	7	10	9	5	8

* 76 observations on 24 different subjects
† 38 observations on 21 different subjects
‡ S.D = Standard deviation

TABLE 2 —*Cardiac Output Values in Resting Normal Human Subjects*

	Surface Area, M²	Cardiac Index,* L min M²	Stroke Index,† cc /beat/M²
Average values	1 89	3 5	46
S D	0 17	0 7	8 1
Extreme values			
upper	2 15	5 3	63
lower	1 66	2 5	37

* Cardiac index = cardiac output/M^2 of body surface area
† Stroke index = stroke volume/M^2 of body surface area

TABLE 3 —*Pulmonary Resistance in Resting Normal Human Subjects*

	Dynes sec cm⁻⁵		
	R_s*	R_p†	R_{pv}‡
Average values	1130	205	67
S.D	178	51	23
Extreme values			
upper	1570	290	106
lower	750	90	44

* R_s = Total systemic resistance, average values for 23 subjects.
† R_p = Total pulmonary resistance, average values for 22 subjects
‡ R_{pv} = Pulmonary vascular resistance, average values for 20 subjects

and left ventricle. When ejection occurs into an easily distensible system, such as the normal pulmonary vessels, the magnitude of both the absolute values and the phasic changes in pressure (the pulse pressure) is small. The normal values in man for pressures recorded from the right side of the heart and pulmonary vessels in this laboratory by Barratt-Boyes and Wood[1] are given in TABLES 1, 2 AND 3 A typical record of pulmonary artery pressure is shown in FIGURE 1, and that figure also shows that the contours of the recorded pulmonary artery pressure and systemic arterial pressure have certain features in common. The mean level of pressure in the pulmonary artery is related to the volume-rate of flow into the vascular bed, the hindrance to outflow offered by the smaller pulmonary vessels and the pressure in the left atrium

A recording of pulmonary-artery wedge pressure is shown in FIGURE 1. To obtain it, a catheter is advanced until its tip becomes impacted in a small pulmonary artery.[25] Flow through the obstructed segment of lung is small. If the system is considered as static, the pressure recorded from the catheter tip in the wedge position is that of the next portion of the circuit in which normal flow is occurring The pressure so recorded is probably that in the smaller pulmonary veins, which is normally little different from that in the left atrium The left atrial and pulmonary artery wedge pressures in 2 patients with atrial septal defect but without pulmonary hypertension are recorded in FIGURE 3. These curves illustrate the close similarity of these two pressures both in magnitude and contour The tracing of pulmonary-artery wedge pressure normally shows a number of pressure waves (FIGS 1 AND 2), and as indicated in TABLE 1, a wide range of values may be obtained for pulmonary artery wedge pressure in healthy subjects[1] Whether or not this reflects an equally wide range of values in left atrial pressure is unknown at present

Pulmonary venous pressure usually is measured by means of a catheter advanced from the left atrium into a pulmonary vein, the catheter either having been placed in the left atrium by direct puncture or having traversed an interatrial communication. The pulmonary venous pressure may equal or at times slightly exceed the left atrial pressure. The significance of this gradient when present is uncertain, since the diameter of the catheter may approach that of the vein in which it lies and will offer some obstruction to flow of blood along that vein

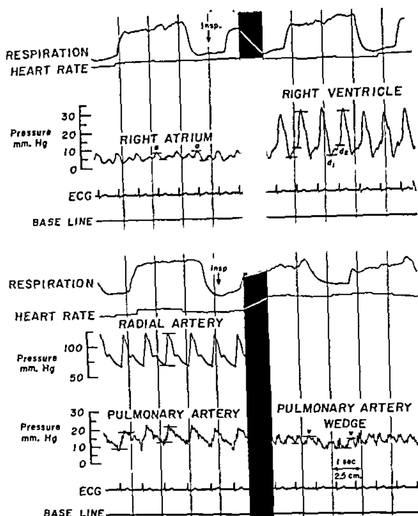


FIG 1 —Pressure pulses recorded at various sites in a healthy woman, 44 years old The right atrial pressure pulse is characterized by a presystolic wave (a) which is usually more prominent than the V wave The A wave is transmitted into the ventricle and is indicated as d_2 in the right ventricular pressure pulse The contour of the pulmonary artery pressure resembles that of the systemic arterial pulse but is characterized by numerous small high-frequency oscillations In the pulmonary artery wedge pressure the A and C waves (not shown) are fused as a single bifid pulse and are followed late in the cycle by a V wave of equal magnitude In normal subjects the V wave may be the predominant wave seen in the pulmonary-artery wedge pressure pulse (Courtesy of the Journal of Laboratory and Clinical Medicine [1])

This is infrequent in man, but not uncommon in the smaller experimental animals

The pulmonary vein wedge pressure (FIG 3) is recorded when a catheter is impacted in a pulmonary vein [9] No blood can escape directly from the particular segment in which the catheter is impacted, but it is possible for the blood entering the segment to leave by collateral venous pathways Again, the segment behaves essentially as a static system and reflects a pressure operative upstream to the point of obstruction. When a catheter is impacted in a pulmonary vein, the recorded pressure is usually somewhat less than that in the pulmonary artery, and its contour usually resembles a damped version of the pulmonary artery pressure pulse

Intravascular pressure represents the force exerted by the fluid within a vessel on the walls of that vessel When the vessel is not changing volume, an equilibrium exists between the force tending to distend it and the forces resist-

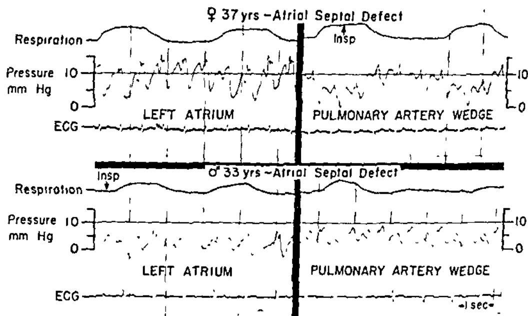


FIG 2 —Comparison of left atrial and pulmonary artery wedge pressures in 2 patients with atrial septal defect [8] Note in each instance the close similarity of the pressure level and the pulse contours The wedge pressure shows a minor degree of damping and some phase lag in comparison to left atrial pressure (Courtesy of the publisher of Circulation Research [8])

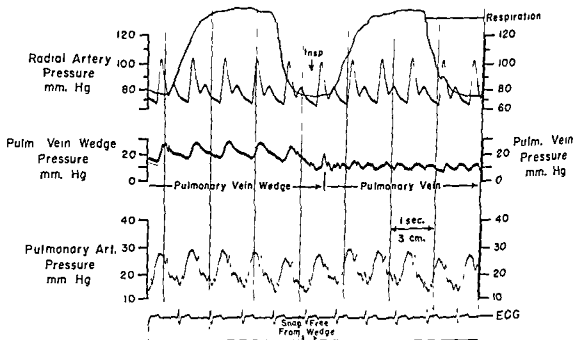


FIG 3 —Pulmonary vein wedge and pulmonary vein pressures with pulmonary artery pressure in a patient who had atrial septal defect and partial anomalous pulmonary venous drainage without pulmonary hypertension Note the similarity both in contour and in magnitude of the pulmonary vein wedge pressure and the pulmonary artery pressure recorded simultaneously When the catheter is withdrawn from the wedge position, a lower pressure which is not significantly different from left atrial pressure is recorded (Courtesy of the publishers of Circulation Research [16])

ing the distention. The forces resisting distention include that contributed by extravascular pressure and that due to tension in the vessel wall associated with its elastic and contractile properties. In the thorax, extravascular pressure varies slightly with respiration, but when a forced expiration is made against a closed glottis, the extravascular pressure will rise considerably. These variations in extravascular pressure are transmitted through the walls of the vessels and directly affect the recorded intravascular pressure. The values given in TABLE 1 are mean values recorded during normal respiration. The caliber of the vessels is influenced fundamentally by the difference between the intravascular and extravascular pressures, this difference is known as "the transmural pressure."[18] When the pressure is low, as in the pulmonary circulation, the influence of extravascular pressure must be taken into account. In practice, extravascular pressure cannot be measured directly but intra-esophageal pressure provides an approximate measure in the intact subject.

Pulmonary Blood Flow

Although accurate measurements of phasic changes in pressure are easily attainable, attempts to measure phasic changes in blood flow during the cardiac and respiratory cycles have begun only recently. The parameter usually referred to as pulmonary blood flow is the average blood flow over a period of time which may vary from one-half to four minutes depending on the technic used for this measurement. In practice, average flow determined in this way has considerable value in the study of the pulmonary circulation.

The two methods in common use are the Fick principle applied to oxygen exchange and the indicator-dilution method.

The Fick Principle Applied to Oxygen Exchange

This method is based on a general relationship between the rate of flow through a system and the rate of transfer of a substance into this system, together with the difference in concentration of the substance on either side of the point of its transfer. This is stated in terms referable to oxygen transfer in the pulmonary circulation.

$$Qp = \frac{V_{O_2}}{Cpv_{O_2} - Cpa_{O_2}} \qquad (1)$$

in which Q_p represents pulmonary blood flow, V_{O_2} the volume of oxygen consumed per unit of time, and Cpv_{O_2} and Cpa_{O_2} represent the concentration of oxygen in pulmonary vein and pulmonary artery blood respectively. In recent years, the assumptions underlying such calculations have been examined in some detail. Applied to the estimation of oxygen transfer, Fick's equation can be precisely stated for infinitesimal intervals of time

$$\frac{dV_{O_2}}{dt} = [Cpv_{O_2}(t)\ Qpv(t)] - [Cpa_{O_2}(t)\ Qpa(t)] \qquad (2)$$

Reduction of equation 2 to the usable form given in equation 1 necessitates integration of the variables to the right of the equation with respect to time, assuming that $Qpv = Qpa$ and that Qp, Cpa_{O_2} and Cpv_{O_2} do not vary with time. Since these assumptions are not fulfilled in biologic systems, the validity of such calculations has been questioned.[35]

Fishman and associates[16] have discussed the problems of stability of respiratory metabolic equilibrium. Constancy of oxygen consumption, the respiratory exchange ratio (RQ) and emotional stability have been used as the criteria of a "steady state." Visscher and Johnson[40] considered the effect of sampling blood at a constant rate through a needle or catheter in relation to the question whether the sample of blood so obtained contains the same mean concentration of oxygen as the volume from which the sample was taken. If concentration is constant, no problem exists, but when both concentration and flow vary, sampling at a constant rate may not give a sample of the same mean oxygen content as that of the blood passing the sampling site during the period of collection. In practice, this error is probably small.[36] The attainment of a steady state of ventilation, circulation and gas exchange is probably more important. For comparative measurements under a changed physiologic state, such as the effects of exercise, drugs or acute hypoxia, a reasonable period must be allowed to permit

readjustment of the gaseous distribution within the body before samples of blood or gas for the *determination of pulmonary blood flow* are collected.

The Stewart-Hamilton Indicator-Dilution Method

The indicator-dilution technic is a variant of the Fick principle A known quantity of identifiable material is injected into the circulation, and the changing concentration of that material is measured at a point downstream. Flow in the vascular system is calculated from the equation [23]

$$Qp(\text{L/min}) = \frac{60I}{\bar{c}t} \qquad (3)$$

in which I is the quantity of material injected in milligrams, $\bar{c}$ is the average concentration of the material in milligrams per liter at a point in the circulation for the time (t in seconds) which is taken for all the material to pass that point once

When the indicator enters the circulation, it is diluted by blood in the chambers of the heart and in the pulmonary vessels Furthermore, dispersion of indicator results from the variation in time required for blood to traverse paths of differing lengths through the lungs and from the longitudinal dispersion that occurs in association with flow through tubes (FIG. 4) The theory underlying the application of this method to the measurement of blood flow has been clearly presented by Meier and Zierler [31] This probably can be most simply understood with reference to FIGURE 5 A known quantity of indicator is introduced at point A, traverses the complex circuit and appears at B in a dispersed form. The concentration curve depicted below the schematic circuit shows a rise to a maximal concentration followed by a decline to the zero value as the indicator is washed past the sampling site The total area subtending the dilution curve excluding that part due to dye particles which have once passed through the systemic capillaries recirculated through the lungs and reappeared at the sampling site may be numerically represented by $\bar{c}t$ and is used in equation 3

The principal assumptions underlying the application of indicator dilution to measure-

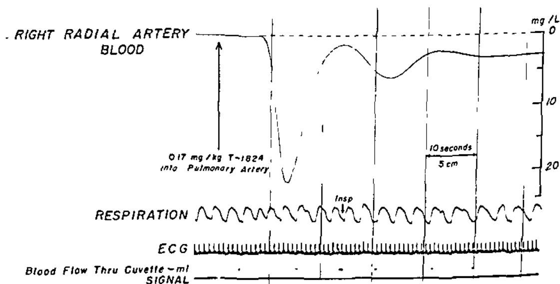


FIG 4 —Indicator-dilution curve obtained from the systemic arterial blood in a normal subject (a woman, 44 years old, weighing 59 Kg) to show the dispersion of indicator injected into the pulmonary artery Increasing concentrations are depicted as a downward deflection. Following the main deflection, a secondary deflection of somewhat reduced amplitude can be seen to peak approximately 18 seconds following the first peak This portion of the curve is due to indicator which has traversed systemic capillaries and again reappears at the arterial sampling site for a second time The influence of recirculated indicator must be excluded

ment of flow may be summarized as follows: (1) There is no loss of indicator from the system. (2) Flow remains constant during the dilution of indicator and inscription of the curve. (3) Since the flow measured applies only to that of the fluid with which the indicator mixes, the measurement of the total flow requires that fluid from all upstream pathways and all the indicator injected meet and be completely mixed at some point in the circuit.

Turning now to the practical application of this method, the most useful indicators currently available are indocyanine green (Cardio-Green*[19]) and Evans blue.* These nontoxic water soluble substances are retained within the vascular system for at least one complete circulation of blood. They differ in that Cardio-Green absorbs light most effectively in the infrared region of the spectrum (at about 810 millimicrons), whereas Evans blue has a peak absorption in the red region (about 640 millimicrons). Detectors for the continuous recording of the concentration of both of these dyes in flowing blood are currently available.† Evans blue has a particular disadvantage when continuous recording of the concentration of dye by densitometry is used, in that changes in the absorption of light caused by variations in the quantity of reduced hemoglobin in the blood stream cannot be distinguished by the detecting instrument from changes in concentration of dye. Use of Cardio-Green circumvents this problem.

For accurate application, a steady-state is required for three to five minutes for the oxygen-Fick method and for 10 to 20 seconds for the dye-dilution method. The accuracy of the dye-dilution method in the determination of mean pulmonary flow may be more vulnerable to the normal physiologic variations in flow, such as occur during the respiratory cycle, but from the practical standpoint, it has many advantages. Possible errors of measurement are reduced since the determination depends on a single time-concentration curve only. Estima-

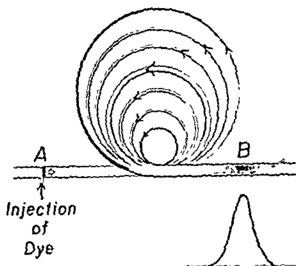


FIG 5.—Schematic representation of the central circulation to illustrate the dispersion of dye in the vascular system following its injection in a single bolus at point A. After traversing the complex circulation the indicator is dispersed according to the frequency of pathways of differing traversal times. This dispersion is inscribed as a time-distance curve in the outflow from the system (B). If a continuous sample of the blood-indicator mixture is drawn at any point in the outflow (B) and the rate of sampling is constant relative to the flow past the sampling point, then a curve of similar contour will be obtained—a time-concentration curve. (For discussion of calculation of cardiac output, see text.)

tions may be repeated at intervals of about two minutes, and 40 or more determinations of cardiac output have been made in a single experiment. A more extensive discussion of the problems associated with the determination of pulmonary blood flow by the oxygen-Fick or dye methods is outside the scope of this chapter, and for details of technic the reader may refer to descriptions in numerous other texts. Under most circumstances values for pulmonary blood flow may be obtained by either of these methods that permit interpretation of changes of the order of ±20 per cent in the volume rate of blood flow through the lungs. TABLE 2 shows the values for cardiac output (total pulmonary blood flow) for normal human subjects determined by the oxygen-Fick method.

The total flow of blood reaching the left heart includes not only the blood which originated from the right ventricle but also a small contribution from the bronchial arteries. The

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† Gilford Instrument Laboratories, Elyria, Indiana. Medical Division, Waters Corporation, Rochester, Minnesota.

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The Stewart - Hamilton Indicator - Dilution Method

The indicator-dilution technic is a variant of the Fick principle. A known quantity of identifiable material is injected into the circulation, and the changing concentration of that material is measured at a point downstream. Flow in the vascular system is calculated from the equation.[23]

$$Qp(\text{L/min}) = \frac{60I}{\bar{c}t} \qquad (3)$$

in which I is the quantity of material injected in milligrams, $\bar{c}$ is the average concentration of the material in milligrams per liter at a point in the circulation for the time (t in seconds) which is taken for all the material to pass that point once.

When the indicator enters the circulation, it is diluted by blood in the chambers of the heart and in the pulmonary vessels. Furthermore, dispersion of indicator results from the variation in time required for blood to traverse paths of differing lengths through the lungs and from the longitudinal dispersion that occurs in association with flow through tubes (Fig. 4). The theory underlying the application of this method to the measurement of blood flow has been clearly presented by Meier and Zierler.[a] This probably can be most simply understood with reference to Figure 5. A known quantity of indicator is introduced at point A, traverses the complex circuit and appears at B in a dispersed form. The concentration curve depicted below the schematic circuit shows a rise to a maximal concentration followed by a decline to the zero value as the indicator is washed past the sampling site. The total area subtending the dilution curve excluding that part due to dye particles which have once passed through the systemic capillaries recirculated through the lungs and reappeared at the sampling site may be numerically represented by $\bar{c}t$ and is used in equation 3.

The principal assumptions underlying the application of indicator dilution to measure-

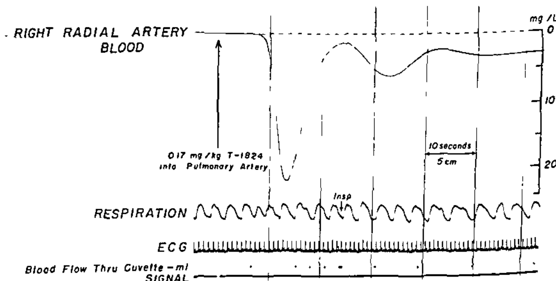


Fig. 4.—Indicator-dilution curve obtained from the systemic arterial blood in a normal subject (a woman, 44 years old, weighing 59 Kg.) to show the dispersion of indicator injected into the pulmonary artery. Increasing concentrations are depicted as a downward deflection. Following the main deflection, a secondary deflection of somewhat reduced amplitude can be seen to peak approximately 18 seconds following the first peak. This portion of the curve is due to indicator which has traversed systemic capillaries and again reappears at the arterial sampling site for a second time. The influence of recirculated indicator must be excluded before calculation of blood flow can be carried out from the dilution curve.

pressure to mean flow. The equation of Poiseuille describes the uniform flow of a simple liquid through a straight, smooth-walled, non-distensible, circular tube. This equation states:

$$Q = \frac{(P_1 - P_2)\pi r^4}{8\mu L} \qquad (8)$$

in which Q is the steady rate of flow of the liquid of viscosity μ, $P_1 - P_2$ indicates the difference in pressure at two points a distance (L) apart in the tube of radius (r). Rearranging this equation it can be seen that

$$\frac{P_1 - P_2}{Q} = \frac{8\mu L}{\pi r^4} \qquad (9)$$

In this system, the viscosity of the fluid and the geometry of the tube are the variables which affect the ratio of pressure difference to flow. It is true that Poiseuille's equation does not strictly apply to the biologic vascular system in which flow is pulsatile, the viscosity of blood is anomalous, and the vessels are distensible and are characterized by branching and changes in caliber. However, provided certain limitations as clearly reviewed by Lilienthal and Riley[30] and by others are recognized, this ratio is of value in assessing the behavior of vascular beds. Changes in the pressure-flow ratio may be cautiously interpreted as evidence of changes in the geometry of the vascular bed, i.e., a fall is suggestive of vasodilatation and a rise, of vasoconstriction.

In the normal pulmonary circulation, changes in the pulmonary pressure-flow ratio are more difficult to interpret than in the systemic circulation, since for the same flow rate, the pressure drop across the pulmonary vascular bed is approximately one-tenth that across the systemic vascular bed. In other words, the hindrance offered by the pulmonary vessels is a fraction of that offered by systemic vessels, and this is due to a difference in structural geometry of the two systems.

Two "resistance" values are calculated for the pulmonary vascular bed. The first is known as the total pulmonary resistance (Rp or TPR) and is given by the equation.

$$Rp = \frac{\bar{P}pa}{Qp} \qquad (10)$$

in which $\bar{P}pa$ represents the mean pulmonary artery pressure. This value is related to the total hindrance encountered by blood passing from the pulmonary artery to the left ventricle in which the end diastolic pressure is assumed to be zero.

The second value is known both as the pulmonary "vascular" resistance (Rpv) and as the pulmonary "arteriolar" resistance (PAR) and is calculated from the equation:

$$R_{pv} = \frac{\bar{P}pa - \bar{P}la}{Qp} \qquad (11)$$

in which $\bar{P}_{la}$ represents the mean left atrial pressure. This value is related to the hindrance offered by the pulmonary arteries, arterioles, capillaries, venules and veins to the blood flowing from the pulmonary artery to the left atrium. Since direct measurement of left atrial pressure is not always practical, the mean pulmonary artery wedge pressure is frequently substituted in its place. The term "pulmonary vascular resistance" is to be preferred since, at least in the normal pulmonary circulation, the contribution to this hindrance by vessels downstream to the pulmonary arterioles is probably significant. However, in patients with pulmonary hypertension associated with increased pulmonary vascular resistance, a great proportion of the increased resistance is indeed at the level of arterioles or small arteries.

Perhaps to emphasize the empirical nature of these calculations, some authors disdain the use of physical units of force and prefer to use a simple ratio of mean pressure in millimeters of mercury divided by mean blood flow in liters per minute (resistance-units). Alternatively, and to no advantage, pressure in centimeters of mercury may be converted to dynes per square centimeter by multiplying by 13,320 (gravitational constant [984 cm./sec.^{2}] times relative density of mercury [13.54]), and divided by flow in milliliters per second. Thus,

$$R(\text{dynes sec. cm}^{-5}) = \frac{\bar{P}(\text{mm. Hg}) \times 1332 \times 60}{Q(\text{L./min.}) \times 1000} \qquad (12)$$

Although the physical justification for this conversion is dubious, resistance is commonly expressed in this fashion. TABLE 3 gives the values

volume of the latter usually is thought to be approximately 1 per cent of the total pulmonary blood flow but may be considerably increased in disease states Since blood from the bronchial arteries has not been mixed with that in the proximal pulmonary arteries, samples taken from the main pulmonary artery may not yield a precise measure of the mean oxygen content of the blood reaching the pulmonary capillaries Hence, theoretically, the contribution of the bronchial blood flow will not be detected in the conventional application of the Fick method, but will be included when pulmonary blood flow is measured by the dye-dilution method However, accuracy of measurement of this order is well outside the limits of either method The volume-rate of pulmonary blood flow traversing pulmonary arteriovenous shunts or alveolar capillaries in poorly ventilated regions will be included in an estimate of pulmonary blood flow by either the Fick or the dye methods

Pulmonary Blood Volume

The terms "pulmonary blood volume" and "central blood volume" as used in the current literature may refer to a volume very different from that contained in the pulmonary blood vessels This applies particularly to the volume calculated from the formula

$$Vp = Qp \times \bar{t} \qquad (7)$$

in which V_p is the pulmonary blood volume or central blood volume and $\bar{t}$ is the mean transit time or the average interval required for indicator particles to travel from the injection site to the sampling site In theory, if indicator were injected into the main pulmonary artery and were sampled from the left atrium, the pulmonary blood volume could be measured with reasonable accuracy, but the necessary condition that the blood sampled from the left atrium be representative of that flowing through all the pulmonary vascular pathways is difficult to attain with certainty. However, the left ventricle and aortic root together form an efficient mixing chamber, and the volume of blood contained in the vessels of the lung and chambers of the left side of the heart may be calculated from indicator-dilution curves recorded from the aorta or one of its branches. The volume measured when injection and sampling sites are still further removed from the central circulation is easier to define than to visualize in its anatomic setting. When sampling is carried out from the aorta or its branches, the volume of blood in the arterial system at positions temporarily equivalent to the point from which the blood-indicator mixture is sampled is also included in the estimation When injection of indicator is made at positions upstream to the root of the pulmonary artery, the volume of blood in the right heart and in the venous system from points temporarily equivalent to the position of injection is likewise included To the present, the calculations of pulmonary blood volume based on peripheral sampling or sampling at injection sites or both represent approximations of dubious value, and directional changes, such as those reported to occur during exercise, may be positively misleading One method of obtaining a reasonable approximation of the true pulmonary blood volume is to use the difference in volumes calculated from two dilution curves made after dye is injected into the main pulmonary artery and left atrium in turn; sampling in both cases is done from the same systemic artery—preferably one close to the aortic root Unlike the calculation of flow, accurate calculation of volume from an indicator-dilution curve requires a sampling and recording system of high dynamic response, since any delay in recording events at the sampling site will produce an apparent increase in the mean transit time

Sjostrand[35] considered that the venous side of the pulmonary circulation provides a large capacity for the storage of blood and may be more important as a blood storage depot than are the systemic veins in accommodating rapid adjustments in left ventricular output in response to body needs However, Hamilton[22] concluded that changes in end-diastolic volume in the ventricles are of more importance in this respect than the changes in the capacity of the lung vessels

Resistance

In hemodynamics the term "resistance" usually refers to a ratio of mean differences in

serotonin is the most potent pulmonary vasoconstrictor studied to the present, whereas norepinephrine and in some animals epinephrine have a definite, but moderate vasoconstrictive action It was not possible to demonstrate consistent pulmonary vasodilatation with acetylcholine, but Borst and associates suggested that this was due to the dilated state of the normal pulmonary vascular bed.

Studies on the influence of vasoactive agents on the normal pulmonary circulation in man are more meager. Goldenberg and associates[21] found a fairly consistent increase in the mean pulmonary artery pressure during infusions of norepinephrine and of epinephrine However, the former agent caused no significant change in cardiac output, whereas the latter invariably caused an increase Since these workers did not measure the left atrial or pulmonary artery wedge pressure, no certain conclusion could be reached as to whether or not constriction of pulmonary vessels had occurred. Fowler and associates[15] reported that in their experiments the pulmonary artery wedge pressure rose equally with pulmonary artery pressure during infusion of epinephrine. However, Patel and associates[32] demonstrated an increased gradient across the pulmonary vessels during infusions of norepinephrine with no significant change in blood flow and left atrial pressure. Their data appear to indicate active constriction of pulmonary vessels in response to norepinephrine

Since epinephrine increases cardiac output, it is more difficult to be certain of its effect on the pulmonary blood vessels The observations of Hamilton and associates[24] on dogs suggest that epinephrine has no direct effect on the pulmonary blood vessels, and the data of Goldenberg and co-workers[21] are compatible with an unchanged pulmonary vascular resistance during infusion of epinephrine.

The effect of vasodilator agents in normal man is unclear Infusions of acetylcholine have been shown to reduce the pulmonary vascular resistance both in normal subjects rendered hypoxic[20] and in patients with various forms of pulmonary hypertension, but it has not been possible to demonstrate vasodilatation in the human lung at normal levels of tone

The effects of drugs on the pulmonary vascular bed can be summarized as follows. (1) Constriction of the pulmonary blood vessels can be produced in most mammalian species studied, including man (2) Agents found to be vasoactive in regard to the pulmonary circulation may have a much greater or even an essentially different effect on the peripheral blood vessels. (3) There may be a difference between species in regard to both specificity and sensitivity. (4) The most potent constrictor of pulmonary blood vessels yet studied is 5-hydroxytryptamine (in the dog).

The Effect of Altered Oxygen Tension in Inspired Air

Von Euler and Liljestrand[11] demonstrated a rapid rise in pulmonary artery pressure in the cat when the oxygen tension of inspired air was reduced. The work of Fishman and associates[15] and Duke[13] suggests that in man and in the cat, hypoxia increases pulmonary vascular resistance. This effect appears to be confined to the lung that is ventilated with the gas mixture of low oxygen tension. The data concerning canine pulmonary vessels are less clear-cut because of variability in the published results but suggest the same response as in the cat [27]

The mechanism and site of action of hypoxia and drugs is not known The vessels affected may be the small arteries and arterioles, the capillaries of the postcapillary vessels. In regard to 5-hydroxytryptamine, the site of action is probably the precapillary vessels, but there is evidence that the increased pulmonary vascular resistance associated with the injection of Escherichia coli endotoxin into dogs and the resulting pulmonary edema are due to constriction of pulmonary veins.[27]

The Behavior of the Pulmonary Vascular Bed Under Physiologic Conditions

The evidence that the pulmonary vascular bed exhibits vasomotion under the influence of extreme hypoxia and certain drugs sheds little light on the normal regulatory mechanisms The pulmonary circulation is a low resistance circuit, and there is normally only a mean gradient across the pulmonary vascular bed of 5 to 7 mm. Hg in contrast to a gradient of about 75 mm. Hg for the systemic circulation. Since the pressure gradient is small, extravascular pressure and hydrostatic considerations greatly

for total systemic resistance and pulmonary vascular resistance in normal human subjects.

Pulmonary Vascular Resistance and Transmural Pressure

Values of pulmonary vascular resistance (*Rpv*) may be used to provide a rough comparison of the caliber of the pulmonary blood vessels between different subjects or to indicate a change in the vascular geometry in an individual. Interpretation of changes may be possible only when other dynamic variables remain relatively constant. Of these changes, the transmural pressure is important. Particularly when changes in vessel tone are under consideration, changes in this value may permit some conclusion as to the reaction of the blood vessels. A decrease in *Rpv* associated with a decrease in transmural pressure suggests vasodilatation, whereas an increase in *Rpv* with an increase in transmural pressure suggests vasoconstriction. However, a decrease in *Rpv* with an increase in transmural pressure or an increase in *Rpv* with a decrease in transmural pressure might be best interpreted to imply that these changes in resistance are the mechanical consequences of the changes in transmural pressure.

The Regulation of the Normal Pulmonary Vascular Bed

While the mechanisms regulating ventilation are relatively well understood, those concerned with the perfusion of the lung with blood are less clear. The remainder of this chapter is concerned with the basic question of whether there is active regulation of the caliber of pulmonary blood vessels or whether the vessels are passive, their dimensions being determined solely by the transmural pressure.

The possibility of active regulation is suggested by the observation that the walls of pulmonary arteries and veins contain innervated smooth muscle.[29] Furthermore, the available evidence seems to indicate that the pulmonary vessels constrict in response to hypoxia and to certain drugs. However, one cannot conclude on this basis alone that even a part of the pulmonary vascular bed is normally under constant vasomotor control. Relevant data, therefore, must be considered in two parts: that related to the demonstration of reactivity of these vessels, and that concerning the behavior of the pulmonary bed under physiologic conditions.

Reactivity in Normal Pulmonary Blood Vessels

Most evidence for vasomotor activity in the pulmonary vessels depends on the correct interpretation of changes in pulmonary vascular resistance. Variables of importance which influence the caliber of vessels other than vasomotion include the pressure gradient across the pulmonary vascular bed, the pulmonary blood flow, the left atrial pressure, the extravascular pressure and probably also the volume of the lung. Therefore, if the pressure-flow ratio is to be used as a valid index of caliber of the vessels, the effect of an agent can be interpreted with greater certainty when other variables remain unaltered or change minimally. Even under these circumstances the technical difficulties of simultaneous and accurate measurement of pulmonary blood flow and of the small pressure gradient across the normal pulmonary vascular bed are considerable. Changes of the order of 30 to 50 per cent in the pressure-flow ratio are needed before one can conclude that significant changes in vascular caliber have occurred. Confidence in the significance of smaller changes is increased when either the pressure gradient or the blood flow is held constant. Since this method is applicable in practice only to experimental animals, such preparations have been the basis for much of the more conclusive work on the reactivity of the pulmonary vascular bed. Knowledge obtained from these experiments adds significance to studies in man which necessarily have been less well controlled.

The Effect of Pharmacologic Agents Injected into the Pulmonary Circulation

Among many workers, Borst and associates[4] controlled flow and pressures in the canine pulmonary circulation by replacing the right ventricle with a pump and perfusing each lung separately at constant flow. 5-Hydroxytryptamine caused a considerable rise in the pressure in the pulmonary artery, indicating vasoconstriction. Animals were found to vary in their response to epinephrine, whereas norepinephrine regularly caused vasoconstriction of moderate degree. These authors concluded that

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affect the flow of blood through any part of the lung.

During inspiration, there is a simultaneous increase in the transmural pressure and blood flow that is consistent with passive dilatation of the pulmonary vessels.[6] Furthermore, the flow through, and the transmural pressure in, the vessels in the lower parts of the lung are greater than in the upper parts, due to hydrostatic effects.[2] Both these observations suggest that the caliber of normal pulmonary vessels is greatly influenced by simple mechanical factors. Recent studies suggest that the vasoconstrictor effect of hypoxia in one lung can be largely overcome by the small increase in transmural pressure which occurs when the patient lies with that lung down.[3]

The effect of exercise has been studied chiefly in the human. Donald and associates[12] found that during graded exercise the gradient across the lungs (pulmonary artery pressure minus assumed left atrial pressure) increased to the same degree or to a greater degree than the pulmonary blood flow. This suggests that the pulmonary vessels were not dilating in response to the increased pressure within them. However, a different response was found by Marshall and associates[34] and by others in the unanesthetized dog. They found that the pressure gradient increased only a little with large increases in blood flow. Furthermore, these workers observed no major change in the volume of blood between pulmonary artery and aortic root. They concluded that a considerable dilatation of the precapillary vessels had occurred. Whether this resulted from a passive dilatation due to the slight increase in pulmonary artery pressure or from a reflex dilatation of these vessels has not been determined.

Comment

It is evident that regulation of the pulmonary vascular bed is incompletely understood. The evidence that the normal plumonary vascular bed responds to sympathomimetic and parasympathomimetic agents suggests that it is possible for the autonomic nervous system to affect the pulmonary vessels. Under what circumstances this may occur is unknown, but recently Daly and Daly[11] demonstrated a reflex pathway in dogs by which stimulation of the carotid sinus induces pulmonary vasoconstriction. Little is known of the relative potency of the various stimuli which may affect the pulmonary vascular bed, and it is possible that significant active vasomotion occurs only in circumstances of extreme physiologic stress.

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ter The measurement of pulmonary arterial pressure requires more difficult technical procedures such as right heart cardiac catheterization or needle puncture of the pulmonary artery.

Pulmonary hypertension may be associated with levels of pressure ranging from slight increases above the normal to levels exceeding those normally present in the systemic circulation. The highest levels of pulmonary blood pressure are seen in mitral stenosis and in essential pulmonary hypertension.

Another difference between pulmonary and systemic circulation is that the level of pulmonary blood pressure may be affected by alterations in bronchomotor tone For example, histamine increases pulmonary vascular resistance primarily by a constricting action on the bronchi [4]

A simple classification of pulmonary hypertension may be given as follows

Primary (essential or idiopathic)
Secondary
- Increased pulmonary venous pressure
  - increased left ventricular diastolic pressure (left ventricular failure, hypervolemia).
  - obstruction to left atrial outflow (mitral stenosis, myxoma of the left atrium, cor triatriatum)
  - pulmonary vein stenosis
- Due to obstruction to flow in the pulmonary arteries (embolism, thrombosis, pulmonary emphysema, fibrosis, metastatic carcinoma)
- Associated with congenital heart disease and left-to right shunting

Pulmonary wedge pressure in studies of pulmonary hypertension. In physiologic studies of patients with pulmonary hypertension, an important observation can be made by right heart catheterization and determination of the pulmonary "capillary" or wedge pressure, since this usually varies with the pulmonary venous pressure [25] This pressure is obtained by wedging a cardiac catheter into a small branch of the pulmonary artery in the peripheral lung field The validity of the measurement is checked, first of all, by the peripheral position of the catheter tip, second, by observing that the tip moves less than normally with each cardiac beat, third, from the change in the pressure curve as noted in the pulmonary artery; fourth, aspiration from the catheter yields blood which is completely saturated with oxygen in the absence of severe pulmonary disease or yields no blood; and, finally, by the fact that the tip of the catheter tends to be difficult to withdraw and may snap back several centimeters when it is withdrawn. Determination of the pulmonary wedge pressure may be of value in distinguishing between pulmonary hypertension due to left ventricular failure or mitral obstruction, on the one hand, in which elevation of the wedge pressure would be expected,[10] and between pulmonary hypertension due to chronic lung disease[21] or essential pulmonary hypertension,[6] in which the pulmonary wedge pressure would be expected to be normal Measurement of the pulmonary wedge pressure does not distinguish between pulmonary hypertension due to left ventricular failure, on the one hand, and that due to mitral stenosis on the other. It may be necessary to measure the gradient of pressure across the mitral valve by left heart catheterization or to observe the effect of digitalis on pulmonary arterial pressure elevation to make this distinction An increase in the diastolic pressure gradient across the mitral valve would establish mitral stenosis as the cause of increased pulmonary arterial and venous pressure, whereas its absence would indicate left ventricular failure as the likely cause. Ferrer and co-workers[18] demonstrated that the administration of intravenous digoxin lowered the pulmonary arterial pressure in left ventricular failure but did not affect pulmonary arterial pressure in patients with mitral block.

Pulmonary Hypertension in Mitral Stenosis

Mechanisms of pulmonary hypertension in mitral stenosis A simplified diagram of the effect of mitral stenosis on pulmonary arterial pressure is shown in Figure 1, which indicates the elevation of left atrial and pulmonary venous pressure due to the mitral block, and the secondary increase in pulmonary vascular resistance, tending to increase still further the pulmonary arterial pressure. Ferrer has pointed out that there are at least three factors which may be contributory to pulmonary hypertension in mitral stenosis.[15] First of all, the block at the mitral valve results in an increase of

Impairment of the Pulmonary Circulation

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THE PULMONARY CIRCULATION IN GENERAL

THE pulmonary circulation in the human adult is a low resistance system in comparison with the systemic circulation. The mean arterial blood pressure in the pulmonary circulation, which averages about 15 mm Hg, is approximately one-sixth of the mean systemic arterial blood pressure[20] Since blood flow through the systemic and lesser circulations is equal and the left atrial pressure is somewhat higher than right atrial pressure, the resistance of the pulmonary circulation is approximately one-tenth that of the systemic circulation

The pulmonary circulation is adaptable to moderate flow increases without elevation of mean arterial pressure if the lungs and pulmonary vascular bed are normal The removal of one lung in an animal or patient is not associated with significant elevation in pressure at rest in the remaining pulmonary artery even though the flow of blood through that artery is approximately doubled.[8] It is assumed under these circumstances that initial resistance in the remaining lung is within normal limits With exercise the pulmonary flow may increase approximately three times normal before an increase occurs in pulmonary arterial pressure[7, 26] These observations imply that increase of pulmonary blood flow in the normal lung is associated with decline in pulmonary vascular resistance, since it is unlikely that left atrial pressure or intrathoracic pressure declines during exercise sufficiently to explain the failure of pulmonary arterial pressure to rise in the presence of increased flow.

The absence of valves in the pulmonary veins is of considerable importance in relation to pulmonary hypertension associated with mitral stenosis or left ventricular failure[5, 16] Thus, significant obstruction to flow from the left atrium to the left ventricle whether it be caused by mitral stenosis, cor triatriatum,[15] or myxoma[30] of the left atrium may be associated with pulmonary hypertension because of elevation in the pulmonary venous pressure, pulmonary capillary pressure and, thus, of pulmonary arterial pressure. Similarly, failure of the left ventricle, due to elevation of the diastolic pressure produces an increase of left atrial pressure and in turn affects the pulmonary venous and pulmonary capillary pressure

The small pulmonary vessels are supplied by the sympathetic and parasympathetic nerve fibers[9] The pulmonary veins contain smooth muscle, nerve fibers and ganglionic cells[31] Thus, the autonomic nervous system may play some part in increasing pulmonary resistance when there is elevation of pulmonary venous pressure

Pulmonary hypertension, in general, has certain differences from systemic hypertension As for example, most instances of systemic hypertension are considered to be essential in type and cannot be ascribed to a known primary disease Pulmonary hypertension, on the contrary, is usually secondary to a primary disease of the heart or lungs and is most commonly associated with either left ventricular failure, mitral stenosis or pulmonary disease Only a few cases of pulmonary hypertension are considered to be primary or idiopathic[16], the actual existence of essential pulmonary hypertension has been questioned.[29] Another important feature of pulmonary hypertension is that the blood pressure in the pulmonary circulation is affected by an increase of pressure in the left heart, whereas the systemic blood pressure is not appreciably affected by increases of pressure in the right heart.

From the clinical viewpoint, another distinction between systemic and pulmonary hypertension is the fact that the level of the systemic blood pressure may be estimated with some accuracy by use of the sphygmomanome-

arterial pressures from 40 to 69 mm. Hg had moderate pulmonary hypertension; and in patients with 70 mm. Hg or above were classified as having severe pulmonary hypertension.

Physical signs of pulmonary hypertension in mitral stenosis. A prominent a wave in the jugular vein was found by Whitaker in all patients who had mean pulmonary arterial pressure above 52 mm. Hg although 4 of 11 patients with normal sinus rhythm and pulmonary arterial pressures of 50 mm. Hg or higher had no prominent a wave. A history of paroxysmal nocturnal dyspnea or hemoptysis was noted not infrequently in patients with severe pulmonary hypertension and in cases with mild or moderate pressure elevations. These observations were rarely helpful in predicting the level of pulmonary arterial blood pressure.[19] A left parasternal lifting impulse in systole is a valuable sign of right ventricular enlargement. This was found in our studies and those of Whitaker at many levels of pulmonary arterial pressure. This observation was of little value, therefore, in estimating the level of pulmonary arterial pressure. The pulmonic second sound was classified according to intensity into four groups by Whitaker: (1) normal, (2) pulmonic second sound louder than the aortic, (3) loud split pulmonic second sound and (4) fixed split pulmonic second sound with accentuation of the second component. In Whitaker's study, the split pulmonary second sound with accentuation of the second component was noted only in patients with moderate or severe pulmonary hypertension; a normal pulmonic second sound was elicited only in those with mild hypertension. The Graham-Steell murmur was defined by Whitaker as a short, early-diastolic murmur, maximal in the third and fourth left intercostal spaces following a loud pulmonary second sound in association with mitral stenosis and occurring in the absence of peripheral signs of aortic insufficiency. This murmur was heard only at mean pulmonary arterial pressure levels of 34 mm. Hg or above and was fairly consistently heard at pressures of 70 or above (7 of 8 cases). However, the difficulty in distinguishing this murmur from mild aortic insufficiency without peripheral signs renders it of doubtful value in estimating severity of pulmonary hypertension.

Electrocardiogram in mitral stenosis with pulmonary hypertension. One of the most helpful studies in our work as well as that of Whitaker's was the presence of electrocardiographic evidence of right ventricular hypertrophy which may be defined simply as an R or RS pattern in Lead V_1 associated with inversion of T in V_1. This pattern was noted fairly consistently by Whitaker with one exception, at mean pulmonary arterial pressures of 50 mm. Hg and above, but not observed at mean pressures of 40 mm. Hg or below. In our study, the electrocardiographic findings of right ventricular hypertrophy were not found with the mean pulmonary arterial pressure below 28 mm. Hg, but were noted, with one exception, when pulmonary arterial pressures were above 42 mm. Hg.[27] In another study by Scott and co-workers from our laboratory,[28] the electrocardiographic pattern of right ventricular hypertrophy with mitral stenosis was usually associated with a pulmonary "arteriolar" resistance of 1,000 dynes second/cm^5 or approximately eight times normal.

Roentgen evaluation of pulmonary hypertension in mitral stenosis. Whitaker considers that cardiac enlargement (x-ray) occurs only with pulmonary hypertension in mitral stenosis. In our study[19] and that of Ferrer,[17] there was no correlation between over-all cardiac size and the level of pulmonary arterial pressure in mitral stenosis. Whitaker concluded that the right pulmonary artery was prominent at levels of 40 mm. Hg and above and not at levels below 33 mm. Hg Whitaker pointed out that the prominence of pulmonary artery was helpful in suggesting pulmonary hypertension if one could exclude atrial septal defect, ventricular septal defect and patent ductus arteriosus. Abrams[1] has indicated the value of comparing the size of the right descending pulmonary artery with the size of a peripheral pulmonary artery in the adult. He believes also that the diameter of the right descending pulmonary artery of 17 mm. or more suggests enlargement due either to increased flow or pulmonary hypertension; if the ratio of size of right descending pulmonary artery to peripheral pulmonary artery is greater

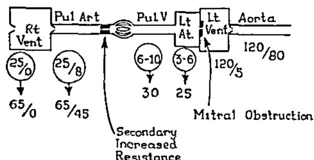


FIG 1—Diagram of the mechanism of pulmonary hypertension in mitral stenosis

pulmonary venous pressure in order to maintain satisfactory blood flow According to Gorlin and co-workers[24] the normal resting mitral valve flow is capable of increasing the pulmonary venous pressure when the area of the valve orifice is less than 2 5 cm², the normal being 4 to 6 cm.[2] Many patients with severe symptomatic mitral stenosis have a mitral valve orifice area of between 0 5 and 1 cm² A second factor is the increase in the pulmonary vascular resistance seen in certain patients with mitral stenosis having greater elevation of pulmonary arterial pressure than pulmonary venous pressure This implies increased resistance to flow of blood in the pulmonary circulation itself The site of this increased resistance, whether it be pulmonary arteriole, capillary or vein, is not known Dexter[10] has postulated that at a pulmonary "capillary" pressure level of 25 mm Hg or above in mitral stenosis or in left ventricular failure there occurs a progressive increase in pulmonary vascular resistance to protect the lungs against further increase in pulmonary capillary pressure which would lead to pulmonary edema. This mechanism is not universally accepted and has been questioned by Cournand and associates[7] and by Lukas and Dotter[28] A third factor in the pulmonary hypertension that may be noted in patients with rheumatic heart disease and mitral stenosis is that of left ventricular failure presumably due to associated myocarditis, mitral insufficiency or aortic valve disease. As has been mentioned earlier, Ferrer and associates[18] have employed the response of pulmonary arterial pressure to intravenous digoxin to distinguish between pulmonary hypertension associated with mitral valve block and that associated with left ventricular decompensation.

The pulmonary hypertension of mitral stenosis may be decreased by autonomic ganglionic blocking drugs,[2, 34, 42] by acetylcholine infusion[39, 40] and by breathing 100 per cent oxygen.[13] Wood[39] considered that mitral stenosis may be classed into groups of reactive and passive types, the reactive type having increased pulmonary vascular resistance in addition to elevation of pulmonary venous pressure The vasospasm, according to Wood, may be partially alleviated by acetylcholine

It should be added that the level of pulmonary arterial pressure is also affected by the heart rate in patients with elevation of pulmonary venous pressure due to mitral stenosis Tachycardia shortens the time available for diastolic flow across the mitral valve, thus necessitating higher pulmonary venous pressure to maintain flow.

Smith, Burchell and Edwards[35] have described medial and intimal thickening of small muscular pulmonary arteries, arterioles and veins in patients with mitral stenosis The authors postulate that these changes are secondary to obstruction to pulmonary venous outflow and may be protective against pulmonary edema

Clinical evaluation of pulmonary hypertension in mitral stenosis As mentioned earlier, the estimate of the degree of pulmonary hypertension usually depends on direct pulmonary arterial cannulation However, Whitaker[38] and Fowler and associates[19] have studied the correlation between clinical evidence of pulmonary hypertension and the level of pulmonary arterial pressures in mitral stenosis It would seem from these studies that one may predict with a fair degree of accuracy the level of pulmonary arterial pressure in patients with mitral stenosis Whitaker studied 25 patients with predominant rheumatic heart disease and rheumatic mitral stenosis for correlation between pulmonary arterial pressure and the electrocardiograms, x-rays and clinical evidence of pulmonary hypertension. The pulmonary arterial mean pressures in his group were from 16 to 108 mm Hg of Mercury. He considered that patients with mean pulmonary arterial pressures of less than 40 mm. Hg had mild pulmonary hypertension, those with mean pulmonary

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than 8, pulmonary hypertension is probably present; if the ratio of right descending pulmonary artery diameter to peripheral pulmonary artery diameter is less than 6, a significant increase of pulmonary blood flow is probably present Prominence of the transverse lines of Kerley do not, according to Abrams, imply elevation of pulmonary arterial pressure but rather an elevation of pulmonary venous pressure. Thus, in pulmonary hypertension unaccompanied by mitral stenosis, Kerley lines are almost invariably absent whereas in pulmonary hypertension associated with mitral stenosis they are frequently present [1] An example of Kerley's lines in a chest x-ray of a patient with rheumatic mitral stenosis and pulmonary edema is seen as transverse lines in the right costophrenic angle in FIGURE 2A FIGURE 2B shows disappearance of the lines after cardiac compensation; the large left atrium may be seen through the right heart border in FIGURE 2B.

It should be pointed out that the evaluation of the pulsations of the small branches of the pulmonary artery by fluoroscopy may be helpful since these would not be expected in mitral

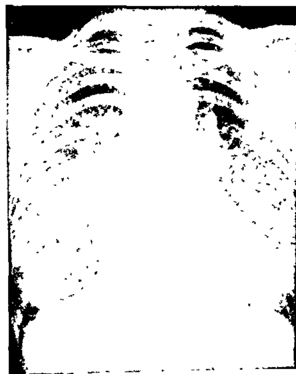


FIG 2.—(A) Pulmonary congestion and Kerley's lines in rheumatic mitral valvular disease



FIG 2 —(B) Clearing of pulmonary congestion and disappearance of Kerley's lines in same patient as in FIGURE 2A

stenosis but may occur in pulmonary hypertension associated with left-to-right shunts, as seen in atrial septal defect, ventricular septal defect or anomalous pulmonary venous drainage In our experience, we have not seen these pulsations with increased pulmonary blood flow due to patent ductus arteriosus

Treatment The treatment of pulmonary hypertension accompanying mitral valvular stenosis consists of surgical relief of the block. This assumes there are no contraindications: significant aortic valvular disease, predominant mitral insufficiency, bacterial endocarditis, left ventricular failure and clinically evident, active rheumatic fever. Studies of pulmonary arterial pressures in patients subjected to satisfactory mitral commissurotomy display in most instances, not only a decrease in left atrial and pulmonary "wedge" pressure but also a decrease in the secondarily elevated pulmonary vascular resistance.

As stated above, pulmonary hypertension accompanying mitral stenosis may be partially reversible A 25 year old woman whom we stud-

ied seven years ago had pulmonary arterial pressure of 80/30 mm Hg in association with rheumatic mitral stenosis Two months postoperatively her pressure was 45/21. Pulmonary wedge pressure was reduced from 24 to 14 mm. Hg. This patient may have developed later still greater reduction in pressures since maximum reduction may not take place for many months according to Ferrer and associates.[16] In FIGURE 3 are shown electrocardiograms of a 31 year old man with rheumatic mitral stenosis. These were taken before and after mitral commissurotomy. FIGURE 3A, a preoperative record, shows broad notched P waves of left atrial enlargement in standard Leads I and II, right axis deviation of QRS and the pattern of right ventricular hypertrophy in lead V_1. Note the diminution of the electrocardiographic signs of *left atrial and right ventricular hypertrophy* in the electrocardiogram of FIGURE 3B, taken 8 months postoperatively

Werko and associates[37] have pointed out that the pulmonary arteriolar resistance in mitral stenosis may be reduced to normal following a mitral commissurotomy However, in Werko's study, these postoperative patients showed an abnormal response to exercise, increasing their pulmonary arterial pressure abnormally with moderate increases in pulmonary blood flow.

PULMONARY HYPERTENSION IN MITRAL INSUFFICIENCY

It should be pointed out that rheumatic mitral insufficiency may be associated with pulmonary hypertension Bentivoglio and coworkers[4] have shown that a considerable degree of pulmonary hypertension occurs *in patients* with mitral insufficiency, and in a study of 65 patients with mitral incompetency the predominant lesion, there was electrocardiographic evidence of right ventricular hypertrophy in 15 per cent of cases. Bentivoglio and his group[3] also reported 4 patients with *mitral incompetency* who had pulmonary hypertenison. These workers postulated that increased resistance to dilation by the left atrium might result in transmission of the regurgitant left ventricular wave into the pulmonary vascular bed, thus activating a mechanism for pulmonary hypertension. The pulmonary arterioles and veins *showed in*timal thickening and narrow lumina in these patients.

PULMONARY HYPERTENSION DUE TO ATRIAL MYXOMA, COR TRIATRIATUM OR PULMONARY VEIN STENOSIS

Paquet[30] reported 4 cases of atrial myxoma, 2 involving the left atrium and 2 the right atrium The diagnosis of left atrial myxoma is suggested by the following findings: mitral stenosis without rheumatic etiology; postural changes in the mitral diastolic murmur, especially if it becomes more prominent on sitting or standing, progressive heart failure unimproved by the usual therapy. *One patient seen* by the author was more dyspneic on sitting up than lying down, probably because the erect position led to greater occlusion of the mitral orifice. In one case of left atrial myxoma, Paquet reported a pulmonary wedge pressure of 35 mm. Hg and mean pulmonary arterial pressure of 54 mm. Hg, indicating moderate pulmonary hypertension The roentgen and clinical findings were consistent with mitral stenosis.

The diagnosis of atrial myxoma can be made before surgical exploration by histologic examination of a peripheral embolus, demonstrating myxomatous tissue, or by angiocardiogram showing a filling defect of the left atrium. It may be difficult, however, to exclude a large atrial thrombus as a cause of the filling defect.

The recommended treatment of atrial myxoma is surgical removal, since these tumors are usually pedunculated and benign. Successful operations were not described at the time of Paquet's report [30]

Edwards and co-workers[15] have reported obstruction to pulmonary venous return with cor triatriatum as a cause of right ventricular hypertrophy and pulmonary arteriolar changes similar to those seen in mitral stenosis. In this rare condition, the pulmonary veins empty into a small accessory chamber, which communicates with the left atrium through an opening of variable size Edwards and Burchell[14] described pulmonary hypertension in association with acquired partial pulmonary vein obstruction. The small pulmonary arteries showed medial thickening and fibrous intimal disease

than 8, pulmonary hypertension is probably present, if the ratio of right *descending* pulmonary artery diameter to peripheral pulmonary artery diameter is less than 6, a *significant* increase of pulmonary blood flow is probably present Prominence of the transverse *lines of Kerley* do not, according to Abrams, imply elevation of pulmonary arterial pressure but rather an elevation of pulmonary venous pressure. Thus, in pulmonary hypertension unaccompanied by mitral stenosis, Kerley *lines* are almost invariably absent whereas in pulmonary hypertension associated with *mitral stenosis* they are frequently present [1] An example of Kerley's lines in a chest x-ray of a patient with rheumatic mitral stenosis and pulmonary edema is seen as transverse lines in the right costophrenic angle in FIGURE 2A FIGURE 2B shows disappearance of the lines after cardiac compensation; the large left atrium may be seen through the right heart border in FIGURE 2B.

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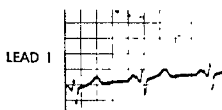
Pulmonary Hypertension Due to Atrial Myxoma, Cor Triatriatum or Pulmonary Vein Stenosis

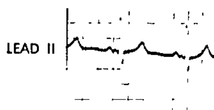
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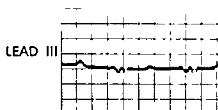
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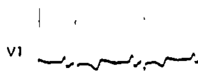
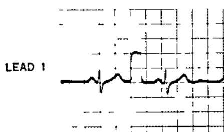
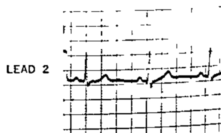
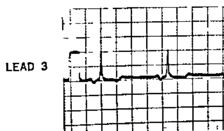


Fig 3—(A) ECG showing evidence of left atrial enlargement and right ventricular hypertrophy in a 31 year old man with rheumatic mitral stenosis Note right axis deviation, broad notched P wave in leads I and II, and tall R wave in lead V_1.







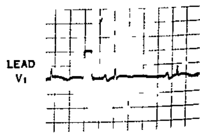


Fig 3—(B) ECG from same patient as in Figure 3A, eight months after mitral valvotomy Note disappearance of signs of left atrial enlargement and diminution of R wave in lead V_1.

only in the lobes drained by the obstructed pulmonary veins.

Pulmonary Hypertension in Left Ventricular Failure

Mechanism. Pulmonary arterial hypertension and elevation of pulmonary "capillary" pressure due to left ventricular failure was described by Dexter.[10] He also demonstrated the association of increased pulmonary vascular resistance when the pulmonary "capillary" pressure became elevated, as is shown diagrammatically in Figure 4. There is also noted in Figure 4 the increase of left ventricular diastolic pressure in left ventricular failure, leading to increased pressure in the left atrium and pulmonary veins. Secondary increase in pulmonary vascular resistance may also occur, resulting in further increase of pulmonary arterial pressure. Failure of the left ventricule is the most common cause of pulmonary hypertension As mentioned previously, the pulmonary "capillary" or wedge pressure is elevated in pulmonary hypertension due to left ventricular failure as distinguished from the lack of elevation in pulmonary hypertension due to lung disease or essential pulmonary hypertension. Ferrer and associates[18] have shown that pulmonary hyper-

and stroke volume In contrast, digitalization with intravenous digoxin in patients with hypertension due to mitral block associated with rheumatic mitral stenosis had no effect on the level of pulmonary arterial pressure or on cardiac output.

Ferrer and associates have demonstrated in patients with cor pulmonale and congestive heart failure that administration of intravenous digoxin produced an increase in pulmonary arterial pressure with increased stroke volume.[18] The pulmonary arterial pressure rose because of an increased cardiac output associated with a fixed pulmonary vascular resistance. Kelley and co-workers[27] showed that administration of 30 mg hexamethonium in 15 patients with left ventricular failure, 8 of whom were hypertensive, produced in 2 instances a fall in pulmonary arterial pressure. There was a decline

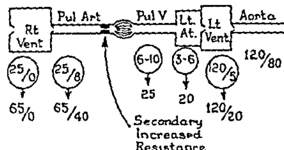


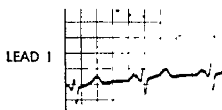
Fig 4.—Diagram of the mechanism of pulmonary hypertension in left ventricular decompensation.

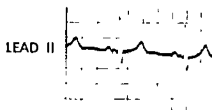
in the elevated systemic venous pressure where previously it had been increased. The circulation time shortened in 8 of 12 patients and the vital capacity improved in 5 of 11. It is difficult to know whether the fall in pulmonary arterial pressure under these circumstances was due to increase in capacity of systemic veins, thus impairing venous return and lowering the cardiac filling pressure on both right and left sides of the heart. Alternative possibilities are additional improvement in cardiac output because of decrease in peripheral arteriolar resistance or a primary effect of hexamethonium on the pulmonary vascular bed to reduce its resistance. Smith and associates[35] have described intimal and medial thickening of small muscular pulmonary arteries, pulmonary arterioles and pulmonary veins in the lungs of patients with left ventricular failure similar to the changes seen in mitral stenosis.

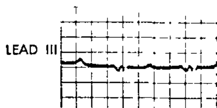
The treatment of pulmonary hypertension due to left ventricular failure is essentially the treatment of congestive heart failure with digitalis, sodium restriction, rest and diuretics being employed if necessary. Reversible precipitating factors should be removed, such as aortic stenosis, hypertension, thyrotoxicosis, beriberi, arrhythmias, systemic arteriovenous fistula, patent ductus arteriosus, ventricular septal defect and severe anemia.

Primary Pulmonary Hypertension

As mentioned previously, essential pulmonary hypertension is an uncommon condition, and the vast majority of instances of pulmonary hypertension are secondary to the disease of the heart or lungs. The subject has recently been reviewed by McGuire and co-workers,[29] who







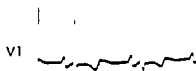
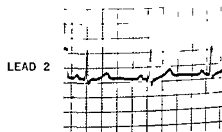
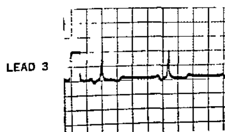


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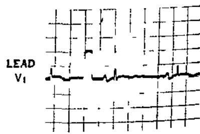


FIG 3—(B) ECG from same patient as in FIGURE 3A, eight months after mitral valvotomy.

Note disappearance of signs of left atrial enlargement and diminution of R wave in lead V_1.

The mechanism of chest pain in these patients may be that of ischemia of the right ventricle due to high right ventricular pressure and interference with right ventricular coronary flow.[12] Viar and Harrison have suggested that dilation of pulmonary artery could be responsible for chest pain as noted in pulmonary hypertension.[26] Essential pulmonary hypertension occurs in various age groups ranging from infancy to late middle life but is most commonly noted in childhood or early to middle adult life. The course of the illness varies from 5 months to 5 years but may continue for 12 years (Chapman[6])

Physical findings in essential pulmonary hypertension The physical findings in essential pulmonary hypertension may be similar to those described in pulmonary hypertension associated with mitral stenosis. The patients often have a loud pulmonary second sound, left parasternal impulse characteristic of right ventricular hypertrophy and a pulmonary systolic murmur. Pulmonary diastolic murmurs were heard in 2 of Chapman's 10 cases,[6] suggesting an associated pulmonary valve insufficiency. An apical presystolic murmur was also heard in 2 instances. This could be due to relative tricuspid stenosis. There was no evidence of systemic hypertension in Chapman's cases; the lungs were clear. Sinus rhythm was found in all of Chapman's cases, with accentuation of the pulmonic second sound in 10 patients.

Laboratory data in essential pulmonary hypertension Cardiac fluoroscopy usually reveals evidence of right ventricular enlargement and prominent pulmonary artery segment. The secondary branches of the pulmonary artery may be dilated but the tertiary branches are small. In one of our patients with probable essential pulmonary hypertension, pulmonary artery enlargement at the hila was mistaken for enlarged hilar lymph nodes. Th-
tion therapy
is shown in F
cated right ventricular hypertrophy in 9 of 10 patients in Chapman's series[6] Routine laboratory procedures are of little diagnostic value, but may show secondary polycythemia in patients with right-to-left shunting through the foramen ovale Pulmonary arterial pressures de-



FIG 6—Chest x-ray of a 50 year old woman with probable primary pulmonary hypertension; pulmonary arterial pressure was 101/41 mm. Hg Note large main branches of pulmonary artery and very small peripheral branches



FIG. 7—Chest x-ray of a woman with probable primary pulmonary hypertension The enlarged left pulmonary artery was originally mistaken for enlarged hilar lymph nodes.

pointed out that a diagnosis of essential pulmonary hypertension necessitates the following considerations It is essential to exclude the usual causes of secondary pulmonary hypertension, *namely*, congenital heart disease with left-to-right shunt, mitral stenosis, left ventricular failure, anoxia associated with pulmonary emphysema and diffuse pulmonary vascular disease, including pulmonary fibrosis, multiple pulmonary emboli and thrombosis of the pulmonary arteries. When the patient has been exposed in an area endemic for schistosomes, pulmonary schistosomiasis must be considered, since this parasitic pulmonary infestation can mimic primary pulmonary hypertension Even though no evidence of the foregoing can be found in clinical examination or cardiac catheterization, it is difficult to accept a case as primary pulmonary hypertension unless an autopsy has been performed excluding not only congenital heart lesions and mitral stenosis but also small emboli and thrombi in pulmonary arteries These may be unassociated with clinical evidence of pulmonary embolism or with pulmonary infarctions as seen on roentgenogram.



Fig. 5—Chest x-ray of a patient with pulmonary hypertension due to multiple pulmonary emboli Note prominence of main branches of the pulmonary artery, with interruption of right descending pulmonary artery.

At present, it is difficult to state whether the occlusive lesions as seen in the small pulmonary arteries of some patients with pulmonary hypertension are secondary to the pulmonary hypertension or are due to multiple small pulmonary emboli. Thus, the pathogenesis of the pulmonary hypertension may remain in doubt after autopsy. An example is noted in Figure 5 of the chest x-rays of a patient who had progressive dyspnea and dilatation of pulmonary arteries over a two year period This patient had pulmonary arterial pressure of 92/22 mm Hg determined by right cardiac catheterization, and there was no clinical evidence of pulmonary disease or left heart disease There was no evidence of pulmonary infarction However, at necropsy multiple occlusions of the pulmonary arteries by emboli were found In Figure 6 is shown the chest x-ray of a woman, 50 years of age, who probably had primary pulmonary hypertension with a pulmonary arterial pressure of 101/41 mm. Hg Note the large primary pulmonary arterial branches in contrast to the small tertiary pulmonary arterial branches in the peripheral lung fields.

Clinical picture of primary pulmonary hypertension Chapman and associates[6] have presented a review of 10 patients considered as having primary pulmonary hypertension, with autopsies in four instances. The history of patients with essential pulmonary hypertension was usually characterized by exertional dyspnea, chest pain which may resemble that of angina pectoris and right heart failure Cyanosis usually was absent initially but occurred later in the course. According to the evaluations, cyanosis does not occur on the basis of poor oxygenation of the blood in the lungs but may result from stagnant anoxia associated with low cardiac output, without causing unsaturation of systemic arterial blood. Another mechanism responsible for cyanosis is that of right ventricular failure and right-to-left shunting through the foramen ovale, which may open because of right atrial dilatation or elevated right atrial pressure These patients may also complain of syncope. The mechanism of syncope is poorly understood, it may be associated with arrhythmias or increasing pulmonary vascular resistance and sudden lowering of cardiac output.

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case, there was some cardiac enlargement Total pulmonary vascular resistance was normal in each of the 4 cases.

Unlike the situation in systemic arteriovenous fistula, the vascular resistance in the lung is normally low, and unless the resistance in the fistula is extremely low, there is no further decrease in pulmonary vascular resistance because of the fistula, and thus no increase in total pulmonary flow. The calculated pulmonary vascular resistance (excluding the shunt) is increased This tends to increase the amount of shunting These patients often have increased blood viscosity because of the polycythemia which frequently is found when there is cyanosis and systemic arterial oxygen unsaturation This polycythemia is of insufficient degree to account for the increase in pulmonary vascular resistance outside the shunt. If the resistance in the shunt is extremely low, then an increase in total pulmonary flow and cardiac enlargement may be found

Treatment of pulmonary arteriovenous fistula The treatment of pulmonary arteriovenous fistula is that of surgical removal This probelm may be difficult in cases of multiple pulmonary arteriovenous fistulae Seventeen of 26 patients operated in the series of Yater[41] were apparently cured In one case, reported by Friedlich,[22] removal of a single lesion caused a rise in oxygen saturation from 68 to 93 per cent of capacity In a second case, oxygen saturation rose from 63 to 97 per cent of capacity on removal of the fistula. In the third case, removal of two fistulae was associated with a fall in hematocrit from 66 to 56, but oxygen saturation remained at 85 per cent and other fistulae still remained. Glenn and associates[23] pointed out that in addition to the dangers of a ruptured fistula and of cerebral thrombosis due to polycythemia, a brain abscess may ensue.

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bosis of major branches of the pulmonary artery.[65]

Pathologic Physiology of Acute Cor Pulmonale

The hemodynamic abnormalities, the clinical picture and the electrocardiographic changes in acute cor pulmonale result from two events: (1) myocardial ischemia, particularly of the right ventricle and posterior wall of the left ventricle and (2) dilatation of the right ventricle resulting from the increased load imposed on this chamber. It is the ultimate inability of the heart to meet these increased demands for work in the presence of relative ischemia that may cause failure and death in acute cor pulmonale.

Mechanism of the production of myocardial ischemia Myocardial ischemia occurs in acute cor pulmonale as a result of reduction in coronary flow, hypoxemia and an increased oxygen requirement of the heart as a result of its increased work. Indeed, acute or subacute myocardial necrosis of varying extent is often seen at necropsy in patients who die in acute cor pulmonale when the myocardial ischemia has been sufficiently severe and prolonged While this necrosis is reported to occur occasionally in the absence of significant narrowing of the coronary arteries it is usually favored by (a) duration of life for several hours or weeks after the initial embolization, (b) pre-existing coronary sclerosis and (c) previous hypertrophy of the heart which accentuated any coronary insufficiency (coronary flow–muscle mass disproportion)[13, 71]

Reduced coronary flow The reduction in coronary flow is due to multiple factors The increased pulmonary resistance causes a rise in right ventricular pressure and dilatation of that chamber. The increased pressures within the right ventricle and often the right atrium, by interfering with the drainage from the Thebesian vessels and the coronary sinus, reduce the effective pressure gradient between the coronary arteries and their drainage systems. The associated increased intramural pressure of the right ventricle acting as an extravascular force further impedes coronary blood flow. Since this reduction of blood flow is most marked in the right coronary artery, the evidence of myocardial ischemia is most marked in the right ventricle and the posterior portion of the left ventricle.[13, 46]

The marked fall in systemic arterial blood pressure which often occurs after pulmonary embolism is frequently disastrous since it further decreases the effective pressure gradient between the aorta and the coronary arteries and their drainage systems. It is due to a combination of events. The immediate systemic arterial hypotension following pulmonary embolization is part of a triad of a Bezold-Jarisch-like reflex (apnea, bradycardia and hypotension) possibly due to the stimulation of pressoreceptors in the heart and lung. Experimentally, it can be abolished by vagotomy.[74] However, the continued hypotension results mainly from the diminished output of the left ventricle which is a consequence of the obstruction to blood flow in the pulmonary circuit (reduced left ventricular inflow).[47] Moreover, this fall in cardiac output per se decreases coronary flow Increased pulmonary venous pressure which has been observed experimentally in pulmonary embolization is known to cause peripheral vasodilatation by a poorly understood mechanism which can be abolished by vagotomy.[74] Prolonged hypoxemia also contributes to the peripheral circulatory collapse.

While not usually recognized clinically, bradycardia develops immediately after embolization. This is a result of a Bezold-Jarisch-like reflex as well as a result of the stimulation of pressoreceptors in the main pulmonary artery trunk.[74] Tachycardia soon supervenes and becomes one of the most outstanding and persistent clinical findings It is a result of the hypoxemia and of reflexes arising from stimulation of carotid and aortic receptors Although initially of compensatory value, tachycardia may lead ultimately to a further reduction in cardiac output and so, secondarily to a diminution of the coronary flow, by encroaching on the rapid inflow phase of the cardiac cycle The existence of so-called pulmonocoronary reflexes in which reflex vagal coronary vasoconstriction is allegedly produced by the sudden obstruction to flow in the pulmonary arteries has not been confirmed[66] A pulmonopulmonary reflex in which pulmonary emboli are accompanied by a

Cor Pulmonale

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Acute Cor Pulmonale

ACUTE cor pulmonale may be defined as acute right heart strain caused by a sudden marked increase in the work demanded of the right ventricle, left ventricular failure being excluded Although the commonest cause of acute cor pulmonale is pulmonary embolism,[65] the two terms should not be used interchangeably since there are other causes for acute cor pulmonale besides pulmonary embolism. In pulmonary embolism, the increased right ventricular work results from an abrupt increase in pulmonary vascular resistance (obstruction) However, the sudden imposition of any increased load (input as well as output) on the right ventricle may cause the identical changes—hemodynamic, clinical, and electrocardiographic—as those occurring in acute cor pulmonale due to pulmonary embolism Thus, acute cor pulmonale has been observed in extensive diffuse disease of the lungs complicated by a sudden further obliteration of the pulmonary vascular bed, as by the supervention of extirpative or collapse surgery, spontaneous pneumothorax, massive atelectasis or extensive pneumonitis [61] Acute cor pulmonale has been reported resulting from acute spontaneous mediastinal emphysema and from a sudden increase in the herniation of intestinal contents through a diaphragmatic hernia A combination of events may lead to acute cor pulmonale. Cases have been described in which compression of a main pulmonary artery trunk or its major branches by a tumor was complicated by the sudden development of a massive pneumonitis or extensive metastases to the remaining pulmonary tissue, they developed fatal acute cor pulmonale [61] The sudden development of a left-to-right shunt will lead to all the abnormalities recognized as acute cor pulmonale. This includes interventricular septal perforation and sudden rupture of an aneurysm of the aorta or sinus of Valsalva into the right atrium, ventricle, or pulmonary artery.

While pulmonary emboli are usually blood clots detached from other portions of the circulatory system (various areas of the venous bed or from the right chambers of the heart), acute cor pulmonale has also been reported due to embolism of air, amniotic fluid, cerebral cortical tissue and fat Acute cor pulmonale will not develop in every case of pulmonary embolism; the number and size of the emboli may be insufficient to cause the acute hemodynamic changes leading to acute cor pulmonale, or the embolization may lead to ventricular fibrillation and sudden death [47]

Elliott and Bemish[24] have pointed out that in the presence of a patent foramen ovale, pulmonary embolism may be followed by right-to-left shunting through the defect which serves to alleviate the effects of the embolism The full clinical sequence consists of pulmonary embolism followed by a variable period of improvement (the "palliative shunt" phase) and finally sudden death when the shunt is occluded In its most recognizable form, the shunt phase is characterized by pallor, cyanosis unrelieved by oxygen, hypotension, profuse perspiration, moderate venous distention and absence of the usual electrocardiographic changes seen in acute cor pulmonale During this phase, peripheral paradoxic embolism may occur because there is a functioning interatrial right-to-left shunt. In their cases, death was precipitated by acute cor pulmonale as a consequence of the sudden obstruction of this decompression shunt between the right and left atria and not to further pulmonary embolism as had been supposed

Patients surviving repeated widespread embolization of the lungs may later develop chronic cor pulmonale.[77] This may occur after repeated multiple small pulmonary embolizations, or after occlusion with subsequent throm-

lobes of the experimental dog produced a reflex vasoconstriction of the perfused lobe although the beads never reached the perfused lobe.[74] However, other observers feel that this type of pulmonopulmonary reflex has not been demonstrated, and that the extent of the pulmonary vascular obstruction will be directly related to the amount of vascular bed occluded.[19, 49]

Elevation of pulmonary venous pressure. There is some evidence that a reflex elevation of pulmonary venous pressure may add to the increase in pulmonary vascular resistance.[51]

Humoral mechanisms. It has been suggested that the liberation of chemical substances such as serotonin at the site of embolism may also act to increase pulmonary vascular resistance. The presence of an increased cirulating serotonin following embolism has been confirmed.[4, 15]

Hypoxemia. Hypoxemia has been shown to cause an increase in pulmonary arterial blood pressure by a mechanism which is described below in the discussion of chronic cor pulmonale.

The development of dilatation of the right ventricle leads to a change in position of the entire heart: clockwise rotation about its longitudinal axis as well as the assumption of a more vertical position.[69]

Electrocardiographic Changes

The electrocardiographic features of acute cor pulmonale (Fig. 1) may be correlated with the two main dynamic alterations just described:

The following electrocardiographic changes may be considered to be a reflection of myocardial ischemia, particularly of the right ventricle and posterior wall of the left ventricle: (1) depression of the S-T junction and segment in Leads 1, 2, aVL, V_5 and V_6 of a type described by McGinn and White as being of the "staircase" variety.[68] Elevation of the S-T

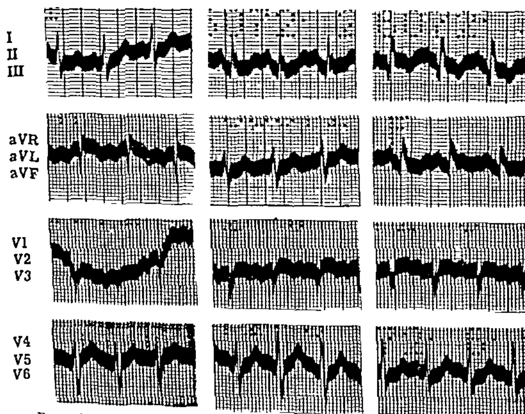


Fig. 1. Acute cor pulmonale [illegible]

reflex vasoconstriction of other branches of the pulmonary arteries without intraluminal obstruction has been demonstrated experimentally and is discussed below

Hypoxemia. Hypoxemia in acute cor pulmonale also results from a combination of causes While the existence of precapillary shunts between the pulmonary arteries and pulmonary veins has been recognized for some time,[99] their possible importance in causing hypoxemia very early after pulmonary embolism has only recently been evaluated Niden and Aviado have demonstrated experimentally that the passage of large glass beads (420 micra in diameter) through these shunts is facilitated by increasing pulmonary arterial perfusion pressure and hindered by ventilation with 100 per cent oxygen The marked lability of these shunts suggests that pulmonary embolism, by increasing pressure in the pulmonary arterial tree, opens them, thus aggravating the concomitant hypoxemia, but at the same time minimizing the rise in pulmonary artery pressure The hypoxemia which is aggravated by these shunts also acts to keep them open[74] Diminished oxygenation of the blood may also occur as a result of a reduction in pulmonary blood flow The peripheral circulatory collapse described earlier favors stagnant hypoxia in the peripheral tissues

Pulmonary edema has been reported in acute cor pulmonale This may result from the peripheral circulatory collapse which may follow acute cor pulmonale, since pulmonary edema has been observed in dogs following acute peripheral blood loss and shock.[23] However, there is also evidence that reflex pulmonary venoconstriction contributes not only to the elevation of pulmonary resistance as described above, but to the production of pulmonary edema as well.[51] Pulmonary edema interferes with the alveolar-capillary diffusion of oxygen and thus also contributes to the hypoxemia.

Increased oxygen requirement of the myocardium The work of the heart in acute cor pulmonale must increase in order to overcome the greater resistance in the pulmonary circuit. Tachycardia may also further tax the heart The oxygen requirement of heart muscle increases at least in proportion to the amount of work performed and the degree of dilatation.[50] This relative ischemia is intensified in the presence of a diminishing supply of oxygen to the heart Significant fever, while unusual as an early manifestation of acute cor pulmonale due to embolism, frequently occurs later and tends to increase the oxygen requirements of the peripheral tissues as well as of the heart.

Mechanism of the right ventricular dilatation. The sudden increase in resistance to pulmonary flow in acute cor pulmonale causes dilatation of the right ventricle and results from the following events

Mechanical obstruction of vessels. The pulmonary emboli may vary in size from the large serpentine embolus, often coiled up, and riding the bifurcation of the pulmonary artery trunk or occluding its main branches, to smaller emboli, occluding the smaller pulmonary arteries or even very minute ones plugging the arterioles The emboli often are detached from their source of origin in volleys In pulmonary air embolism, the catastrophic events result from a different mechanism Death, when it occurs, it due to obstruction of the right ventricular outflow tract by an air trap which forms within it Durant has demonstrated experimentally in dogs that turning the animal onto its left side so that the outflow tract will assume a position inferior to the body of the right ventricle permits the air trap to disappear from this now inferior position, it becomes churned into a froth which gradually disappears from the cavity of the right ventricle by being transported to the lungs with the blood where excretion can take place Thus, displacement of the air trap by turning a patient into the left lateral position may be life saving[22]

Reflex pulmonary arteriolar constriction. Obstruction of small pulmonary arteries and arterioles by showers of emboli is believed to lead to reflex arteriolar constriction, not only in the same lobe but even in the opposite lung[51,71] This parallels the situation seen in embolization of major systemic arteries Additional evidence for this pulmonopulmonary reflex was obtained by Niden and Aviado by using a perfusion technic wherein one lobe of the dog's lung was supplied with blood from a donor dog Injection of glass beads into the unperfused

of the blood supply to a segment of pulmonary tissue, or if a large enough pulmonary artery is occluded, infarcts do occur.[34] When fewer emboli are discharged, instead of true pulmonary infarcts, lesions exhibiting the edema, alveolar hemorrhage and leukocytic infiltration corresponding to the "incomplete infarcts" described by Hampton and Castleman are encountered.[41] The bronchial arterial circulation is an important contributing factor to the development of hemorrhage into pulmonary tissue after pulmonary embolism However, experimentally, if sufficiently severe pulmonary venous congestion is present, pulmonary infarcts develop even after bronchial arteries are occluded to the area before the emboli are produced[25] Since infection frequently helps to cause excavation and the production of infarct cavities, it is important to use antibiotic therapy in patients with pulmonary embolism.

Chronic Cor Pulmonale

Chronic cor pulmonale may be defined as right ventricular hypertrophy resulting from disordered *structure or function* of the lung and/or the pulmonary circulation. Failure of the right ventricle need not be present. This definition excludes such causes of right ventricular hypertrophy as left ventricular failure, acquired valvular heart disease, and congenital heart disease

The true incidence of chronic cor pulmonale has been recognized only recently, cases in the past were overlooked at necropsy as well as in clinical studies. The cachexia of chronic pulmonary disease is often associated with some degree of atrophy of the entire heart so that relative hypertrophy of the right ventricle may be overlooked, relative hypertrophy of the right ventricle can thus be *present* even when the thickness of its wall does not exceed 5 mm , the measurement usually employed to designate hypertrophy Furthermore, it is evident that the absolute thickness of the *right ventricular* wall will be modified by the degree of dilatation present Early technics in which a ratio of left ventricular to right ventricular weight could be obtained, have been further simplified so that the ratio of left ventricular and septum to right ventricular weight can be easily determined.[38, 39] With the employment of this method, a higher necropsy incidence of chronic cor pulmonale is already being reported. In the future, we can expect a true increase in the incidence of chronic cor pulmonale since the newer forms of therapy are permitting a longer survival of patients with chronic pulmonary disease.

Flint[34] report that of 300 patients admitted with congestive heart failure to the City Hospital in Sheffield, England in one year (1952–1953), 64 out of 159 males, and 12 out of 141 females had cor pulmonale. This is equivalent to 40 per cent of the males and 8 5 per cent of the femles. Chronic cor pulmonale was thus found in Sheffield to be the commonest cause of heart failure in males. This incidence is, of course, much higher than it would be in most cities, since Sheffield is a very industrialized community.

In patients with chronic pulmonary disease with a markedly restricted pulmonary vascular bed, the abrupt development of some pulmonary catastrophe, such as extensive pneumonitis, or massive collapse of a lung, which produces a critical increase in pulmonary vascular resistance, may cause a rapid dilatation of the right ventricle associated with myocardial ischemia and death The clinical picture, the electrocardiographic changes and the pathologic findings will be those of acute cor pulmonale, although no pulmonary embolization has occurred[61]

Etiology of Chronic Cor Pulmonale

Chronic cor pulmonale develops only when the pulmonary disease is bilateral and diffuse, rather than unilateral or focal Former classifications have usually been based on the anatomic location of the pathologic process. A more useful classification, more closely related to etiology, is proposed which correlates anatomic and functional abnormalities and, in addition, has important therapeutic implications: Type I—pulmonary disease and dysfunction associated with chronic diffuse obstructive emphysema, Type II—pulmonary disease or dysfunction with chronic alveolar hypoventilation and Type III—pulmonary diseases in which the pathologic process and dysfunction is localized in or about the pulmonary vessels

junction and segment in aVR may also be present. (2) Inversion of the T wave in the precordial leads from the right half of the precordium When inversion is limited to V_2, it may be due to extreme clockwise rotation of the heart When the T wave inversion extends to V_3 and V_4, it may be a reflection of myocardial ischemia or the poorly understood phenomenon of acute right ventricular strain Contrary to the pattern in anterior wall infarction, abnormal elevation of the S-T segments in the precordial leads usually does not occur, except occasionally in V_1 and V_2 (3) Development of a Q wave with *inversion of the* T wave in Lead 3 Contrary to earlier reports in acute cor pulmonale, in Lead aVF a small Q wave may be present (vertical electric position of heart), or absent (semihorizontal electric position of heart) In the latter case the Q_3T_3 pattern is related to the fact that R and T are taller in aVL than in aVF Lead 3 which is roughly equivalent to (aVF-aVL) × $^2/_3$ will as a consequence show a Q and an inverted T Whether the reduction in amplitude of R and T in aVF is partially due to severe ischemia of the diaphragmatic surface of the heart or is merely a result of changes in the heart's position is not known at this time Contrary to the usual pattern in posterior wall myocardial infarction, a Q and an inverted T are not present in Lead 2 The inverted T wave in lead 3 may be the most persistent change in the electrocardiogram [17, 61] (4) *Sinus tachycardia* is almost always present Arrhythmias of almost any type are very frequent They may be reflex in origin They may also be due to ischemia of the myocardium leading to areas which act as *ectopic foci* for the origin of ectopic rhythms or to areas in which conduction is critically slowed to permit the development of re-entry mechanisms which then are responsible for the arrhythmias [62]

The development of sudden dilatation of the right ventricle leads to a change in position of the entire heart: clockwise rotation about its longitudinal axis as well as the assumption of a more vertical position [63] It is this change in position which is responsible for the appearance of deep S waves in Leads 1 and 2 It also causes the shift of the transition zone between right and left ventricular patterns to the left in the precordial leads [61] A so-called incomplete or even complete right bundle-branch system block with a late R may develop in the leads from the right precordium This may appear early or late after the onset of the acute cor pulmonale, it may be transient or permanent. This apparent conduction defect in the right ventricle may be due to the mechanical effect of the sudden marked dilatation of the right ventricle and the ischemia of the right ventricular myocardium P pulmonale, a tall peaked P wave in leads 2, 3 and aVF, may be transiently *present*

The changes described may appear several hours after the episode, and usually disappear after four to ten days. Persistence of the pattern may speak for repeated small pulmonary embolizations [61] The evolution is not prolonged over a period of six to ten weeks as in myocardial infarction

The above description of the changes occurring in acute cor pulmonale is intended to include all of the classic changes It was formerly believed that recognizable electrocardiographic changes could be found in only 10 per cent of cases of acute cor pulmonale Now, with the use of multiple leads and serial records, some changes which would make one suspect the presence of acute cor pulmonale are seen to occur in the majority of cases. However, only by understanding the physiologic mechanisms underlying the *electrocardiographic* changes can one recognize and understand the electrocardiographic picture when it presents itself in a less typical fashion.

Development of Pulmonary Infarction

Nutrient requirements of pulmonary tissue distal to an embolus may be supported by the pulmonary arterial circulation through capillary anastomoses in the pulmonary capillary bed. The bronchial arterial circulation is not necessary for this purpose. It has been observed clinically and confirmed experimentally that pulmonary congestion favors the development of pulmonary infarction after pulmonary embolism However, even in the absence of pulmonary venous congestion, when sufficient emboli are present to produce complete obstruction

diffuse obstructive emphysema, and chronic cor pulmonale have been noted to be more common in males than in females, more frequent in industrial urban areas in the north temperate zones, and in mining regions. Many feel that it is more common among heavy laborers and among heavy smokers.[34, 36]

While cardiac catheterization during status asthmaticus has demonstrated transient pulmonary hypertension, chronic cor pulmonale does not develop in bronchial asthma unless it is severe, associated with recurrent secondary infection, of long duration, and has led to the development of severe diffuse obstructive emphysema.

Severe kyphoscoliosis frequently leads to chronic cor pulmonale. While the major abnormality is chronic alveolar hypoventilation due to anatomic restriction of the chest bellows (see below), these patients suffer from recurrent bronchopulmonary infections which are often perpetuated by interference with bronchial cleansing and a poor tussive mechanism. In many such cases, diffuse airway obstruction, defective intrapulmonary mixing and all the functional and structural abnormalities of obstructive emphysema eventually combine with the restriction of the chest bellows to lead to chronic cor pulmonale.[38, 63, 92]

Chronic cor pulmonale is not infrequently seen when severe diffuse chronic obstructive emphysema has developed as a result of endobronchial tuberculosis and lung distortion by

only when there is diffuse involvement of the lungs. Sarcoidosis, severe enough to cause chronic cor pulmonale, may be of two types. In the first type, the granulomata, being predominantly peribronchiolar and endobronchial, cause diffuse airway obstruction and severe obstructive emphysema. In the second type, the granulomata, located predominantly interstitially and in the interalveolar septa, compress arterioles and capillaries.[3] When changes of this latter type predominate, the patients will fall in the Type III category of chronic cor pulmonale. Not infrequently, a patient will demonstrate changes of both types.

Other causes of obstructive emphysema and cor pulmonale include pneumoconiosis[101] and mucoviscidosis (fibrocystic disease of the pancreas).

Type II. Chronic Alveolar Hypoventilation Syndromes

The important aberration of function in this group is alveolar hypoventilation. This abnormality, in the absence of intrinsic pulmonary disease, when of sufficient severity and duration, leads to hypoxemia, hypercapnia, polycythemia, pulmonary hypertension, right ventricular hypertrophy and right ventricular failure. This group may be further subdivided: (1) conditions associated with impairment of the chest bellows and (2) primary disease (in sensitivity) of the respiratory center. Wherever there is poor functioning of the chest bellows, the cough mechanism and bronchial drainage may be impaired. This often leads to the perpetuation of chronic bronchial infection with the development of diffuse airway obstruction, defective distribution of inhaled air to mixed venous blood and eventually diffuse obstructive emphysema.

Impairment of the chest bellows may result from some chronic neuromuscular disorders such as residual respiratory paralysis following poliomyelitis, the muscular dystrophies, myasthenia gravis and amyotrophic lateral sclerosis.[18, 85] Bellows restriction may also be caused by a thickened inelastic pleura or severe kyphoscoliosis.[53, 42]

A cardiopulmonary syndrome associated with obesity is being recognized with increasing frequency (Pickwickian Syndrome). These patients suffer from anatomic restriction of the chest bellows as well as an increased work of breathing with resultant chronic alveolar hypoventilation and often chronic cor pulmonale.[10, 56]

There have been several reports of patients with normal chest bellows and lungs who demonstrate alveolar hypoventilation secondary to a diminished ventilatory drive from a damaged respiratory center and who eventually develop chronic cor pulmonale.[78, 83] A more detailed discussion of alveolar hypoventilation appears in Chapter 54.

While chronic alveolar hypoventilation is also one of the major functional abnormalities in chronic obstructive emphysema, severe anatomic changes in the lung in this condition are equally important This classification is not rigid since some cases may belong mainly in one category but will demonstrate features of the other Therapy is usually much more satisfactory in chronic cor pulmonale of Type I, than in Type III, because in the first group at least some of the structural and functional abnormalities which caused the development of chronic cor pulmonale are partially reversible [63] This reversibility will be regularly noted in the discussion below.

Type I Pulmonary Disease with Predominant Chronic Diffuse Obstructive Emphysema

Chronic obstructive emphysema is the commonest cause of chronic cor pulmonale in this country. The development, pathology and functional abnormalities in chronic diffuse obstructive emphysema have been reviewed elsewhere Since chronic bronchitis and bronchiolitis, often but not necessarily associated with bronchiectasis, is the commonest cause of diffuse obstructive emphysema, it is therefore also the commonest cause of chronic cor pulmonale in this country [6] Most patients with chronic diffuse obstructive emphysema of the so-called idiopathic type give a history of repeated lower respiratory tract infections with chronic cough and expectoration of many years' duration In such cases, it is quite certain that the chronic bronchial and bronchiolar infection with obstruction has been primary in the genesis of the disease, the loss of pulmonary elasticity being secondary [70, 93] However, occasionally, patients with diffuse obstructive emphysema are encountered, for whom such a sequence does not obtain There is evidence that in such rare cases some poorly understood degeneration of the pulmonary elastic tissue preceded the diffuse airway obstruction, the latter then developing because of interference with ventilation and bronchial cleansing When very large bilateral emphysematous bullae (vanishing lung) are present, they may lead to chronic cor pulmonale mainly by marked compression of relatively normal pulmonary parenchyma However, more frequently, when chronic cor pulmonale develops in such cases, severe obstructive emphysema is found to be present in the rest of the lung. *Chronic bronchial infection,*

TABLE 1.—*Etiology of Chronic Cor Pulmonale*

TYPE I PULMONARY DISEASE WITH PREDOMINANT CHRONIC DIFFUSE OBSTRUCTIVE EMPHYSEMA

1 chronic bronchitis and bronchiolitis, and idiopathic chronic diffuse obstructive emphysema
2 bronchial asthma
3 kyphoscoliosis
4 chronic pulmonary tuberculosis
5 sarcoidosis
6 *pneumonoconiosis*
7 fibrocystic disease of the pancreas

TYPE II CHRONIC ALVEOLAR HYPOVENTILATION SYNDROMES

A Defective chest bellows

1 chronic neuromuscular disorders
2 massive bilateral pleural thickening
3 kyphoscoliosis
4 *cardiopulmonary syndrome* associated with obesity

B Disease of the medullary respiratory center

TYPE III PULMONARY DISEASE WITH PREDOMINANT INVOLVEMENT OF THE VESSELS

Intraluminal processes

1 multiple recurrent small pulmonary emboli
2 primary pulmonary hypertension
3 thrombosis of major pulmonary *arteries*
4 sickle cell anemia
5 schistosomiasis
6 diffuse pulmonary vasculitis

Extraluminal processes

1 sarcoidosis
2 beryllium disease
3 histiocytosis X
4 hematogenous tuberculosis
5 Wegener's granulomatosis
6 collagen diseases
7 diffuse interstitial pulmonary fibrosis
8 idiopathic pulmonary hemosiderosis
9 radiation fibrosis of lungs
10 diffuse interstitial fibrosis caused by chronic obstruction of the pulmonary veins
11 polycystic disease of the lungs
12 pneumonoconiosis
13 metastatic carcinomatosis of lung
14 other diffuse infiltrations of the lung
15 extrinsic compression of main pulmonary arteries

TYPE IV COMBINATIONS OF TYPES I THROUGH III

oles are known to occur in some cases of mitral stenosis, or congenital heart disease with a marked left-to-right shunt.[79] While some investigators have applied the term "cor pulmonale" to such complexes, it would be wise to exclude them from this classification, although the mechanism is similar.

Extraluminal processes. Included in this group are those conditions with extensive infiltration (inflammatory, granulomatous, fibrous or neoplastic) of the interstitial tissues, and particularly the interalveolar septa of the lungs.

The granulomatous interstitial infiltrations of the lung which may result in chronic cor pulmonale include diffuse pulmonary sarcoidosis[14] beryllium disease, histiocytosis X (eosinophilic granuloma)[82] and hematogenous pulmonary tuberculosis.[3] In Wegener's granulomatosis, the extensive vasculitis which is present in addition to the necrotizing granulomatous lesions contribute to the development of pulmonary hypertension and chronic cor pulmonale.[29]

Chronic cor pulmonale has also been observed in scleroderma, where the involvement of the lung has been diffuse and severe. Dermatomyositis and disseminated lupus erythematosus with marked degenerative and occlusive changes in the small pulmonary arteries and arterioles have been reported to cause pulmonary hypertension and right ventricular hypertrophy.[11, 96]

Diffuse interstitial pulmonary fibrosis (Hamman-Rich syndrome) in advanced stages usually results in chronic cor pulmonale.

Chronic cor pulmonale may also result from idiopathic pulmonary hemosiderosis, radiation fibrosis of the lungs, asbestosis, silicosis, metastatic carcinomatosis, farmer's lung, pulmonary interstitial granulomatosis, pulmonary alveolar microlithiasis, pulmonary alveolar proteinosis, and diffuse bronchiolar carcinoma of both lungs. These conditions are discussed in greater detail in Chapter 52.

There have been recent reports of an unusual form of interstitial pulmonary fibrosis due to chronic obstruction of the pulmonary veins. The commonest cause of the pulmonary venous obstruction has been a dense collagenous or keloid-like mass in the mediastinum, apparently a result of a healed posterior mediastinitis. Chronic pulmonary venous obstruction with similar pulmonary changes has also been reported due to a large myxoma of the left atrium, a large left atrial thrombus and congenital stenosis of the pulmonary veins. The extensive pulmonary changes are usually seen only in the portions of the lung whose pulmonary veins have been constricted by the collagenous mass in the mediastinum. Where the process is extensive enough, chronic cor pulmonale develops.[2]

In silicosis, chronic cor pulmonale develops much more frequently when there is the complicating presence of diffuse obstructive emphysema, and here the changes are like those in chronic cor pulmonale due to chronic obstructive emphysema alone, except that the cardiac output tends to be normal or low.[47, 102] However, chronic cor pulmonale has occasionally been recorded in silicosis without significant chronic obstructive emphysema where the silicotic nodules appear to be located mainly about vascular channels, often also with extensive conglomerate scarring.[42] Thrombosis of the major branches of the pulmonary artery frequently occurs in severe silicosis and contributes to the reduction in the pulmonary vascular bed.[102]

Metastatic carcinomatosis of the lung may produce chronic cor pulmonale in several ways. Extensive perivascular lymphatic spread often causes a carcinomatous endarteritis as well as external mechanical compression of the small vessels. Extension into the interalveolar septa may also produce varying degrees of alveolar capillary block. Multiple emboli, composed of either tumor tissue or blood clot from the deep leg veins, may further reduce the pulmonary vascular bed. When the progression of events leading to right heart enlargement and failure is very rapid, the term "subacute cor pulmonale" has been applied.[8, 95]

Combinations of Types I, II or III

There are instances of chronic cor pulmonale developing where changes typical of several of the above categories are present. Examples include sarcoidosis, silicosis and kyphoscoliosis.

Type III Pulmonary Disease with Predominant Involvement of the Vessels

This categroy includes those diseases in which the pathologic changes are mainly localized in or about the pulmonary vessels

Intraluminal processes Among the intraluminal processes are multiple repeated small pulmonary emboli These embolizations may occur over a long period of time, often in the absence of the usual clinical manifestations of pulmonary emboli Eventually, they lead to marked reduction in the pulmonary vascular bed, pulmonary hypertension and chronic cor pulmonale With organization of the emboli, recanalization of many of the vessels will show changes which resemble arteriosclerosis, especially fibrous intimal thickening, they are recognized as emboli only when lung sections are examined carefully.[77] Such cases in the past have frequently been considered examples of primary pulmonary hypertension

Primary pulmonary hypertension is a condition of obscure etiology characterized by progressive right heart enlargement and right heart failure At necropsy, there are no signs of primary pulmonary disease, the advanced cases show extensive changes in the pulmonary arterioles and arteries [21, 49] Disseminated thromboses in the smallest pulmonary vessels are seen but are less extensive than are the sclerotic vascular changes (intimal hyperplasia and occasionally medial hypertrophy) Dresdale[21] considers the sclerotic vascular changes secondary to an already existing pulmonary hypertension, but others believe that the primary abnormality is structural, and perhaps congenital Evans and associates have described some cases which appeared to demonstrate a congenital medial hypoplasia of the muscular arteries, and they postulated that the intimal proliferation occurring as a reparative process initiated the pulmonary hypertension [23] Others have reported instances where the disorder was familial It is quite likely that primary pulmonary hypertension does not represent a homogeneous group but more probably represents a similar end stage picture produced by diverse causes. Primary pulmonary hypertension is discussed in greater detail in Chapter 24

Chronic cor pulmonale may result from massive thrombosis of the major pulmonary arteries. It was recognized quite early that such extensive autochthonous thrombosis of the main pulmonary artery or its major branches was associated with such fibrosing pulmonary diseases as extensive pulmonary tuberculosis or severe silicosis, atherosclerosis of pulmonary arteries, thrombo-angiitis obliterans involving the pulmonary artery, cardiac failure with pulmonary hypertension, and conditions associated with hypercoagulability of the blood However, most of the cases which are now being recognized are secondary to large pulmonary emboli [65] Moreover, the presence of one or more of the disorders which are associated with autochthonous pulmonary artery thrombosis does not always exclude the occurrence of pulmonary embolism but frequently predisposes it to by favoring leg vein thromboses or the spread of secondary thrombosis on an embolus in the pulmonary artery.

Repeated vascular thromboses in patients with sickle cell anemia or sickle-thalassemia may cause chronic cor pulmonale.[73] In these patients, bouts of pleuritic chest pain or unexplained dyspnea, often considered to be pneumonitis, are frequently episodes of pulmonary infarction due to pulmonary arterial or arteriolar thrombosis Since prolonged survival of even severe sicklemic individuals is becoming more common, more instances of this long-range complication of the sickle state will probably become apparent.

Schistosomiasis due to *Schistosoma mansoni* or *haematobium* is a rather common cause of chronic cor pulmonale in Egypt There are massive and repeated infections of the lung with the ova of the parasites, causing an extensive obliterating endarteritis The presence of so-called "angiomatoid" structures are considered to be typical of pulmonary schistosomiasis[3]; their origin is poorly understood. Similar structures have been described in primary pulmonary hypertension [49]

Polyarteritis nodosa may cause chronic cor pulmonale if extensive pulmonary vascular involvement is present Other types of generalized vasculitis may also cause chronic cor pulmonale; the course is usually subacute.

Extensive changes in the pulmonary arteri-

ready restricted pulmonary vascular bed contributes significantly to the pulmonary hypertension. However, whether or not hypoxia causes an increase in resistance to blood flow through the lungs is still very much in dispute. There is disagreement as to the degree to which the pulmonary circulation reflects passively such factors as cardiac output and shifts in blood volume from the systemic to the pulmonary circulation, and the extent of local and neurohumoral mechanisms which actively alter the resistance to flow and thus control, in some degree, the flow through the pulmonary vascular bed.[55] Burton has demonstrated that the pulmonary arterioles are capable of constriction.[9] He produced casts of the pulmonary arterioles, after the administration of rather large amounts of norepinephrine, and demonstrated marked "gnarling" of these vessels, due to contraction of the helical muscles. Further evidence in support of a pulmonary vasoconstrictive factor in man has been obtained by noting the reduction in pulmonary resistance and pressure after the injection of acetylcholine in patients with pulmonary hypertension of many types (except Eisenmenger's syndrome).[103] The evidence now indicates that there are local as well as neurohumoral mechanisms which in response to hypoxia increase pulmonary resistance by an actual reduction in the caliber of the pulmonary vessels. The site of this vasoconstriction is as yet unknown, various investigators having placed it in the pulmonary arterioles, capillaries or venules.[16, 75] Some mechanism must exist to account for the absence of significant venous admixture appearing in arterial blood during periods of minimal ventilation in normal man and in diseased states when ventilation is reduced or abolished in certain areas of the lung.[55] When chronic hypoxia has led to polycythemia, additional factors increasing resistance to pulmonary blood flow are brought into play and are discussed below. The effects of hypoxia are illustrated in FIGURE 2. Hypoxia and its effects are reversible.

5. While there has been suggestive experimental evidence that hypercapnia also contributes to an increase in pulmonary arterial pressure, the extent and the mechanism of this effect are as yet imperfectly understood.[55, 75]

Polycythemia. Secondary polycythemia when present in chronic obstructive emphysema is a result of prolonged hypoxemia. Hypoxemia stimulates erythropoiesis, not by its direct effect on the bone marrow, but by an increase in the production of a plasma erythropoietic stimulating factor (erythropoietin[26]). Marked leukocytosis, thrombocytosis and splenomegaly are not present as they are in polycythemia vera. Secondary polycythemia is associated with an increased blood volume and an increased blood viscosity.

The increased blood volume in secondary polycythemia is due almost entirely to an increase in red cell mass; the plasma volume is usually normal, except in the presence of congestive failure or immediately after recovery from failure. This hypervolemia causes an increased venous return, an increased cardiac output and probably an increased residual volume of blood in the lung. An increase in the residual blood in the lungs in face of an already limited pulmonary vascular capacity may result in a further encroachment on the ability of the pulmonary vascular bed to accommodate an increased blood flow without an increase in pressure. Increased residual blood in the lungs also decreases pulmonary compliance[60] and so would tend to increase the work of breathing. Since satisfactory methods are not available for determining pulmonary residual blood volume, the importance of this factor cannot be evaluated.

The increased viscosity increases the resistance to blood flow in the lungs, but to what extent is unknown. The effect of blood viscosity on the resistance to flow will depend on several factors: the size of the vessels, the rate of flow itself, the character of flow, laminar or turbulent and finally the behavior of a suspension of cells in plasma at various flow rates.[52] Van Liere[100] has shown that an increase of one-third in the proportion of red cells increases the viscosity of the blood three times. However, the viscometer measures blood as though it were a homogeneous fluid. There is probably an axial flow of red cells in the small arterioles, while the plasma moves slowly along the periphery. Moreover, blood having the dynamic characteristics that have been described for pseudo-

Pathogenesis of Chronic Cor Pulmonale

Pathogenesis of Chronic Cor Pulmonale Due to Chronic Diffuse Obstructive Emphysema (Type I)

Of the greatest importance in a discussion of the factors in chronic obstructive emphysema which increase the work of the right ventricle and hence cause its hypertrophy is the degree of reversibility of these elements When therapy is attempted, it is this very element of reversibility which offers hope of improvement The increased load on the right ventricle results from increased resistance to pulmonary blood flow and, when present, from an increased cardiac output.

Increased Resistance to Pulmonary Blood Flow: Increased resistance to the flow of blood through the lungs in chronic obstructive emphysema results from (1) a reduction in the cross sectional diameter and the distensibility of the pulmonary vascular bed, (2) polycythemia (if present) and (3) possibly certain functional consequences of an expansion of intrapulmonary vascular shunts

Reduction in cross sectional diameter and distensibility of the pulmonary vascular bed In man as well as in all higher vertebrates, the pulmonary circulation operates under low pressure with a low resistance to blood flow This low resistance is a result of the large caliber and the marked distensibility of the pulmonary vascular bed. The pulmonary capillaries lack tissue support and are exposed over nearly their entire surface to their environment The fact that only a small increment in pressure occurs with a greatly increased volume of blood flow is of great adaptive significance, since a markedly increased pressure in such a capillary bed would produce a transudate and disturb respiratory function [85] In normal man, in the upright position, pressure in the pulmonary artery remains unchanged, even when the cardiac output is doubled [43] Even with severe exercise, only slight increases in pressure in the pulmonary artery occur. This enlargement of the pulmonary arterial vascular bed results not only from the distension of the individual vessels but also from the opening up of vessels formerly not functioning for flow. The distensibility of the pulmonary vascular bed may be lowered by a reduction in the total number of vessels in the lung (since each vessel contributes its increment of distension), by a reduction in caliber of the vessels and by an increase in rigidity of the individual vessel walls.[63]

Contributing to the reduction in cross sectional diameter and distensibility of the pulmonary vascular bed in chronic obstructive emphysema are the following pathologic changes:

1 Conversion of many small air spaces into fewer larger air spaces and bullae by the rupture of interalveolar septa involves a true destruction of blood vessels In addition, many of the capillaries and vessels adjacent to the bullae are compressed. Air entrapment and hence the size of bullae may be affected by treating bronchial and bronchiolar obstruction

2 Shrinkage of the vascular bed in the lung occurs also in areas of necrosis with replacement by relatively avascular scar tissue, which is frequently supplied by blood from the bronchial rather than the pulmonary arteries

3 Vascular attenuation and diminished distensibility may result from scattered areas of alveolar exudate, atelectasis and air entrapment, all are reversible Cuffing of arterioles by inflammatory exudate and fibrosis will also produce narrowing. Actual thrombosis develops in many of the arterioles, capillaries and sometimes small pulmonary arteries, resolution and recanalization may partially reverse these changes, although subintimal fibrosis often remains Vessel changes secondary to increased intravascular pressure also contribute to the reduction in the vascular bed These include endarteritis obliterans, medial hypertrophy, pulmonary atherosclerosis and occasionally necrotizing arteriolitis. These changes increase resistance to blood flow and hence pulmonary vascular pressure, the latter furthers the secondary hypertensive vascular morphologic changes A vicious cycle thus becomes established Changes in the small vessels are more important than atheromatous changes in the pulmonary arteries, unless the latter lead to thrombosis.

4. Hypoxia increases pulmonary artery pressure [27] It is agreed than an hypoxia-induced increase in cardiac output in the face of an al-

blood does pass through these poorly ventilated areas would have a higher oxygen content, and less pollution of the systemic blood would then occur (2) They increase the blood flow through the lungs, and in the presence of a restricted vascular bed serve to elevate further pulmonary artery pressure (4) They tend to increase the work of the left ventricle, since in effect they are a shunt between the left ventricle and left atrium (4) They may produce an actual reversal of blood flow in the pulmonary artery toward the hilum in some areas, catheterization of patients with extensive bronchiectasis limited to one lung has been shown to yield blood from the pulmonary artery on the affected side that was almost arterial in character.[54]

The existence of anastomoses between the bronchopulmonary veins and the pulmonary veins has long been recognized The smaller bronchi are drained by the pulmonary veins, while the bronchopulmonary veins drain the proximal two to three orders of branches of the trachea and surrounding interstitial tissue. The bronchopulmonary veins drain into the azygos and hemiazygos system, the pulmonary veins into the left atrium. Normally, blood flow across these anastomotic channels is from the pulmonary veins to the bronchopulmonary veins and thence to the azygos or hemiazygos veins This occurs because the pressure in the left atrium is higher than in the right atrium and because of the presence of valves at the site of entrance of the bronchopulmonary veins into the azygos and hemiazygos veins which ensure unidirectional flow When suppuration exists in the lungs causing thrombosis of pulmonary veins, blood is drained away from the area via the anastomoses by the bronchopulmonary veins [54]

In chronic obstructive emphysema, great expansion in the extent and size of these anastomotic venous channels has been demonstrated The causes of this expansion are incompletely understood [54] Liebow has suggested that changes in the respiratory pumping action in chronic obstructive emphysema would affect the true pulmonary venules to a greater extent than the more protected bronchopulmonary venules might favor this expansion of anastamoses Bullae have been shown to represent expanded parts of the respiratory tract more proximal than alveoli, and the venous drainage of these structures is by way of the bronchopulmonary veins rather than by pulmonary veins, just as their arterial supply comes from the bronchial arteries. Also, it has been shown that the walls of bullae contain granulation tissue and much smooth muscle During the formation of granulation tissue these anastomotic channels enlarge and persist even after resolution or cicatrization In chronic obstructive emphysema, an actual reversal of flow in these expanded channels may occur, so that blood would flow from the bronchopulmonary veins to the pulmonary veins This might occur particularly in chronic cor pulmonale with right heart failure where the pressure in the azygos-hemiazygos system will exceed that in the pulmonary veins. In addition, dilatation of the bronchopulmonary veins will cause the stretching of the valve rings at their connections with the azygos or hemiazygos veins, producing incompetency of these valves.[54] Such reversal of blood flow would tend to cause pollution of systemic arterial blood by desaturated hypercapnic venous blood and could thus furnish an important proportion of the venous admixture in the arterial blood.

These expansions of the bronchial arterial and bronchopulmonary venous systems, while clearly demonstrated in chronic obstructive emphysema, have not been quantitatively evaluated

Precapillary anastomoses between pulmonary arteries and pulmonary veins have been demonstrated in normal man but are apparently not extensive enough to be significant under ordinary circumstances [99] However, in acute cor pulmonale, they may be important in contributing to the early hypoxemia which is often overlooked [74] Perfusion of poorly ventilated parts of the lung is equivalent in effect to shunting blood from the pulmonary arterial to the pulmonary venous system.

Cardiac Output. The divergence in the reported studies of cardiac output in chronic cor pulmonale due to chronic obstructive emphysema[29, 35, 42] is explained by the fact the cardiac output at any particular time in these

plastic fluids, exhibits high viscosity at slow rates of flow, lower viscosity at rapid flow. Certainly, therefore, the effect of viscosity will be most marked when the blood flow is at a slow rate and the vessels are reduced in size,[52] the conditions prevailing in patients with chronic cor pulmonale and cardiac failure.

Secondary polycythemia is not invariably present even when there is severe chronic arterial oxygen desaturation. No explanation of this inconsistency has been completely satisfactory.

Secondary polycythemia in patients with chronic obstructive emphysema is an attempt at compensation, not only because the polycythemia leads to an increased oxygen capacity of the arterial blood, but because the hypervolemia, by increasing venous return to the heart, helps to increase cardiac output and maintain a high pulmonary blood flow.[40, 63] Such indeed occurs in normal people exposed to high altitudes, where the adjustment to hypoxemia includes polycythemia and often, also, increased cardiac output. Lewis and associates fear that bleeding a polycythemic subject with chronic lung disease possibly uncovers a state of oxygen unsaturation that may reflect the conditions which originally led to the development of the secondary polycythemia.[52] However, in a patient with chronic obstructive emphysema, at some point the deleterious effects of the polycythemia probably outweigh the possible advantages because of the restricted pulmonary vascular bed. Phlebotomy should be utilized moderately in therapy, always in conjunction with all other therapeutic procedures available to treat the pulmonary disease.

Intrapulmonary vascular shunts. While there is not complete agreement about the extent or even the existence of precapillary anastomoses between the bronchial arteries and the pulmonary arteries in the normal lung,[53, 99] their presence and considerable size have been clearly demonstrated in diseased lungs.

Large and numerous precapillary shunts between the bronchial and pulmonary arteries have been demonstrated in lungs with chronic bronchial infection, tuberculosis and chronic fibrosing disease. Liebow and associates[53] consider that the expansion of these anastomoses is related to their development or enlargement in granulation tissue, in areas of organizing pneumonitis, in the walls of bronchiectatic sacs and in areas of lymphoid hyperplasia and hypertrophied bronchial smooth muscle. They suggest the following consequences of such functioning anastomoses between a high and low pressure system. (1) They might act to shunt desaturated pulmonary artery blood away from poorly ventilated areas of the lung in which they occur to the greatest extent, thus, whatever

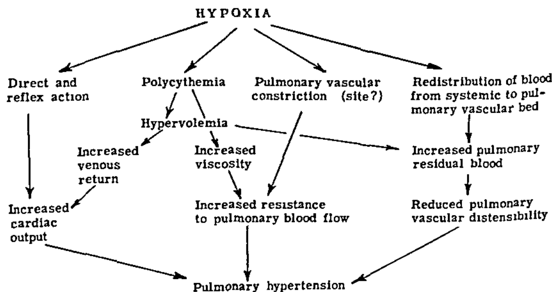


FIG. 2.—Diagram of the role of hypoxia in the development of chronic cor pulmonale.

blood does pass through these poorly ventilated areas would have a higher oxygen content, and less pollution of the systemic blood would then occur. (2) They increase the blood flow through the lungs, and in the presence of a restricted vascular bed serve to elevate further pulmonary artery pressure (3) They tend to increase the work of the left ventricle, since in effect they are a shunt between the left ventricle and left atrium (4) They may produce an actual reversal of blood flow in the pulmonary artery toward the hilum in some areas; catheterization of patients with extensive bronchiectasis limited to one lung has been shown to yield blood from the pulmonary artery on the affected side that was almost arterial in character.[55]

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Cardiac Output. The divergence in the reported studies of cardiac output in chronic cor pulmonale due to chronic obstructive emphysema[20, 25, 42] is explained by the fact the cardiac output at any particular time in these

patients depends on a complex interplay of many variables. The cardiac output depends not only on the type and extent of pulmonary disease present but also on the stage of the disease in which the patient is being studied and will be profoundly affected by the presence of acute bronchitis or pneumonitis, the degree of hypoxia, the severity of polycythemia, the blood volume and, very importantly, the presence and degree of heart failure

The mechanisms which increase cardiac output in chronic cor pulmonale include: (1) exercise, even when mild, (2) hypoxia, (3) the hypervolemia associated with polycythemia, (4) bronchopulmonary infection, with or without fever, and (5) the increased muscular work of breathing shown to be present in chronic obstructive emphysema[76] Should cardiac failure occur at a stage when the cardiac output is elevated, some fall in cardiac output will occur, but the output may still be higher than normal The paradox of "high output failure" is thus explained by the magnitude of the output just preceding failure of the right ventricle[42] When congestive heart failure develops, the increased plasma volume which so often accompanies congestive failure also helps to maintain the cardiac output, however, later, by contributing to the overdistension of the right ventricle, it may help to lower it All of these factors which act to increase cardiac output are potentially reversible by intense treatment, a patient who has a high cardiac output during a desperate stage in his illness may have a normal output after a successful course of treatment

A lower than normal cardiac output may be present in chronic cor pulmonale due to chronic obstructive emphysema if the pulmonary vascular bed is sufficiently restricted with a very high pulmonary vascular resistance The presence of cardiac failure will also result in lowering of the cardiac output

In chronic cor pulmonale with congestive failure, the administration of a rapid acting digitalis glycoside may cause a paradoxical rise in pulmonary artery pressure. This is explained by the fact that digitalis causes an increase in cardiac output and probably better emptying of the failing right ventricle. The resultant increased blood flow through a restricted pulmonary vascular bed causes a rise in pulmonary artery pressure. Acute digitalization will lower the pulmonary artery pressure in patients with chronic pulmonary disease, in whom pulmonary hypertension is caused by left ventricular failure (secondary to arteriosclerotic or hypertensive heart disease). Digitalization may, therefore, help in differentiating pulmonary hypertension due to a reduction in the pulmonary vascular bed from that due to left ventricular failure.[30]

Since intensive treatment of bronchopulmonary disease increases the size of the pulmonary vascular bed, as well as reducing or abolishing hypoxia with its circulatory effects, it is difficult in any specific case to know which abnormality is most responsible for the precipitation of right heart failure Certainly the inhalation of oxygen-rich mixtures which correct arterial hypoxemia may decrease the pulmonary hypertension but do not abolish it[63]

Pathogenesis of Chronic Cor Pulmonale Due to The Chronic Alveolar Hypoventilation Syndrome (Type II)

In this group, chronic alveolar hypoventilation leads eventually to hypoxemia, hypercapnia, polycythemia, pulmonary hypertension, right ventricular hypertrophy and right ventricular failure

In severe kyphoscoliosis, lung volumes, vital capacity and maximum breathing capacity are lowered There is an increase in the work and energy cost of breathing which is partially compensated by a breathing pattern with a small tidal volume and a rapid respiratory rate. This results in a relative increase in dead space ventilation at the cost of alveolar ventilation.[33, 39, 92] While, in many cases, the functional abnormalities may be attributed almost wholly to the alveolar hypoventilation,[33, 88] in other patients, it is to be noted that while some respiratory dysfunction may be present early, severe pulmonary insufficiency and cardiac dysfunction do not appear until much later[64, 92] It is this conspicuous time interval that is the clue to the pathogenesis of the cardiopulmonary abnormalities in these cases The impairment of the chest bellows leads to marked interfer-

ence with bronchial cleansing and, frequently, a poor tussive mechanism It is during this period that repeated episodes of acute and chronic bronchopulmonary infection play havoc with pulmonary integrity and function. Until a better way of quantitating the thoracic deformity and evaluating the natural history in kyphoscoliosis is found, the consequences of *severe* kyphoscoliosis as reported up to now may be classified as follows 1) severe alveolar hypoventilation with resultant hypoxemia, hypercapnia and polycythemia, (2) anatomic restriction of the pulmonary vascular bed with pulmonary hypertension initially resulting only with exercise, (3) impaired distribution of inspired air to mixed venous blood and (4) impairment of bronchial cleansing mechanisms with resulting bronchopulmonary infection and obstruction.

In the cardiopulmonary syndrome associated with obesity, the alveolar hypoventilation results from a reduction in tidal volume, the latter causing a sacrifice of alveolar ventilation to dead space ventilation. The work of breathing is increased because of the marked obesity, and because the expiratory reserve volume tends to be low, the lung approaching the expiratory position Although the entire syndrome appears to be reversible after weight loss, not all obese patients demonstrate these abnormalities The possibility exists that these patients also have some inherent disorder of the central nervous system, possibly of the hypothalamus and the respiratory center.[84]

The rare patients reported with normal chest bellows and lungs but with a diminished ventilatory drive from a damaged respiratory center develop hypoxemia, hypercapnia, secondary polycythemia, right heart hypertrophy and eventually failure They show an absence of dyspnea at rest and during exercise, in spite of the development of severe hypercapnia and hypoxemia These patients show a low ventilatory response to exercise and inspired carbon dioxide. The nature of the damage to the respiratory center is poorly understood but is considered to be inflammatory in some cases, and vascular in others[78, 83]

Pathogenesis of Chronic Cor Pulmonale Due to Pulmonary Disease with Predominant Involvement of the Vessels (*Type III*.)

Intraluminal processes. In this category the marked reduction in the pulmonary vascular bed is the main cause of the very high pulmonary vascular resistance, pulmonary hypertension, and the development of chronic cor pulmonale Physiologic studies have been reported in cases of multiple recurrent small pulmonary emboli, thrombosis of the major pulmonary arteries, and primary pulmonary hypertension. Very little ventilatory dysfunction is usually present. Reduction in the diffusing capacity of the lungs may be explained by the loss of capillary surface area and by the reduced alveolar capillary contact time, associated with the increased velocity of blood flow through the greatly narrowed pulmonary vascular bed.[59] Cardiac output may be reduced, cannot rise with exercise and may even fall. This severe limitation of cardiac output explains much of the symptomatology. Episodic cyanosis frequently is present Occasionally, such cyanosis is associated with a lowered oxygen saturation of the arterial blood, as a result of a right-to-left shunt through a valve competent foramen ovale However, peripheral cyanosis occurs often even when the arterial oxygen saturation is normal with a closed foramen ovale, because a high extraction of oxygen consequent to the reduced cardiac output leads to a high degree of oxygen unsaturation of the venocapillary blood.[91] It is, therefore, not due to arterial hypoxemia Such peripheral cyanosis is noted whenever the systemic blood flow is small in relation to the oxygen utilization of the tissues. Syncope with exertion is not uncommon This symptom has been explained variously (1) a marked fall in coronary blood flow caused by an acute rise in right ventricular pressure; (2) a vasovagal reflex, the impulses arising from receptors in pulmonary arteries, (3) because of the extreme restriction of the pulmonary vascular bed, exercise causes a very great increase in pulmonary artery and right ventricular pressures with consequent acute failure of the right ventricle. The last explanation is probably the correct one and is supported by catheterization studies performed during exercise[49] The restric-

tion of cardiac output also explains the severe exertional dyspnea and weakness Stimulation of receptors in the pulmonary arteries by the marked increase in pulmonary artery pressure accompanying exercise may cause tachypnea, adding to the sensation of dyspnea [4] Precordial pain, usually associated with dyspnea, and not relieved by nitroglycerine may be present It was named hypercyanotic pulmonary angina by Vaquez in 1908 An identical type of chest pain occurs in any condition associated with severe pulmonary hypertension such as mitral stenosis and congenital heart disease Viar and Harrison believe the pain is due to distension of the pulmonary artery. Others feel the pain is due to coronary insufficiency related not only to the severely restricted cardiac output but also to the increase in right ventricular pressure [21]

Extraluminal processes In this group the main cause of the pulmonary hypertension and the chronic cor pulmonale is the great reduction in the pulmonary vascular bed caused by the extensive diffuse interstitial infiltration These cases usually show mild to moderate restrictive ventilatory dysfunction, lowered pulmonary compliance and usually little or no abnormality in intrapulmonary mixing Most characteristic, when the process is severe, is a reduction in the diffusion capacity of the lungs Much of this reduction in the diffusing capacity is due to thickening of the alveolar capillary membrane by infiltration which impedes the passage of oxygen (but usually not carbon dioxide, because it is twenty times as diffusible as oxygen) into the capillary blood.[3, 67] However, it has been pointed out that the diffusing capacity is reduced in many of these cases not merely because of the alveolar capillary block, but also because of the increased velocity of blood flow through a greatly narrowed vascular bed with a consequent critical reduction in the alveolar capillary contact time.[59, 87] These patients often show hyperventilation at rest and during exercise with a low carbon dioxide tension in arterial blood In most of these cases, in the earlier stages, hypoxemia is usually not present at rest, appearing only with exercise If the patient does not die of pulmonary insufficiency, resting hypoxia and sometimes even polycythemia develop so that these will also act to increase the load on the right ventricle as they do in chronic obstructive emphysema.[42] Early in the course of the disease normal or only slightly elevated pulmonary arterial pressure may be present at rest, but exercise will induce significant pulmonary hypertension. While this is probably mainly the consequence of the anatomically narrowed pulmonary vascular channels, some contribution to the pulmonary hypertension must also be made by the exercise-induced hypoxia. Eventually, irreversible resting pulmonary hypertension develops

In chronic cor pulmonale due to diffuse granulomatosis of the lungs or scleroderma, in the absence of resting hypoxia and polycythemia, cardiac output is frequently elevated It has been postulated that this high output in the absence of continual hypoxia is due to the increased metabolism resulting from the active granulomatous inflammation in the lungs,[42] and the increased work of breathing, occasioned by the restrictive ventilatory defect While most of these patients die of pulmonary insufficiency, some eventually develop severe arterial oxygen desaturation and right heart failure, at which time cardiac output is found to be low The pulmonary hypertension in these conditions usually cannot be reversed

The term "Ayerza's Disease" has been used in many ways in the medical literature. Originally, it was a term used by Arrillago, a pupil of Ayerza, to signify a condition in which right heart failure was associated with severe cyanosis, polycythemia (*cardiacos negros*), and pulmonary disease presumed to be syphilitic in origin However, the term has been used to describe a variety of conditions including everything from chronic cor pulmonale due to chronic obstructive emphysema with secondary pulmonary arteriosclerosis, to primary pulmonary hypertension. It would be best if it could be dropped from usage

Diagnosis of Chronic Cor Pulmonale

Since right ventricular hypertrophy is almost impossible to detect early, a definite clinical diagnosis of chronic cor pulmonale is usually made late in the disease While pulmonary hypertension must exist for some time before right ventricular hypertrophy develops, by the time

pulmonary hypertension is detectable clinically in a patient with chronic obstructive emphysema, one may assume that right ventricular hypertrophy is present.

Clinical Findings

Physical examination of the heart helps only in a minority of patients The primary changes in the lungs or in the thorax often make physical examination difficult. The following clinical findings should be searched for: accentuation of the second pulmonic sound, lower sternal dullness, a systolic murmur at the pulmonic area, occasionally a high pitched blowing early diastolic murmur at the pulmonic area. Arrhythmias, with the exception of nodal tachycardia, are unusual. By the time arterial blood gas abnormalities become demonstrable, chronic cor pulmonale may be assumed to be present. The presence of a secondary polycythemia is thus good evidence that right ventricular hypertrophy has already developed and will be found at necropsy. Clubbing of the digits and pulmonary hypertrophic osteoarthropathy do not necessarily indicate the presence of chronic cor pulmonale, since they may occur with very small focal lesions in the lung, such as bronchogenic carcinoma or fibrous mesothelioma They are more frequently present when severe suppurative bronchiectasis coexists with the diffuse obstructive emphysema All the mechanisms involved in the production of clubbing of the digits are as yet poorly understood However, it has been demonstrated that an increased blood flow exists through the clubbed digits which is in excess of physiologic requirements and is largely passing through the numerous arteriovenous anastomoses in the distal segments The direct passage of blood from digital arteries into the deep venous plexus of the digits is held to account for the structural changes observed in clubbed digits [72] However, some feel that clubbing is of endocrine origin. Clubbing is a reversible condition, and in those conditions where a reduction of the circulation to the fingers is possible, regression of the clubbing occurs This has been reported after the removal of pulmonary tumors. Compression of the left recurrent laryngeal nerve by a dilated main or left pulmonary artery may cause left vocal cord paralysis. In those conditions associated with a very high pulmonary artery pressure, as in chronic cor pulmonale due to pulmonary disease with predominant involvement of the vessels (Type III), more striking physical findings may appear. The second pulmonic sound may be intense enough to be palpable. The murmur of pulmonary insufficiency, and occasionally an apical mid-diastolic murmur, corresponding to a "right-sided Austin-Flint murmur" may be present. Because of the low cardiac output, the peripheral pulse is small and systemic blood pressure low, with the systolic and diastolic pressure approaching the mean. Wood has stressed the appearance of giant a waves in the jugular venous pulse.

By the time the usual peripheral findings associated with right ventricular failure are manifest, there can be *no* doubt about the presence of right heart involvement In all cases, the existence of other causes of heart failure must be excluded, particularly arteriosclerotic heart disease Pleural effusions due to the congestive failure are unusual; their presence should alert one to the presence of postpneumonic empyema, or pulmonary infarction. Slight elevation of peripheral venous pressure may be present in chronic obstructive emphysema as a result of the accompanying increased intrapleural pressure. However, when the venous pressure is markedly elevated, right heart failure is usually present.

Roentgenologic Findings

Roentgenologic signs of chronic cor pulmonale, while also rather late in appearing, are suggestive earlier than the clinical findings In addition to the usual roentgenographic studies (posterior-anterior, both oblique, and lateral projections), careful fluoroscopic examination is of special value because it may aid in the simultaneous assessment of pulmonary function.

The earliest abnormal change is enlargement of the main pulmonary artery and its major branches The former is best seen in the right anterior oblique or lateral projection (Fig. 3A). Diffuse obstructive emphysema usually causes specific changes in the position of the heart, the heart becoming more vertical and rotated

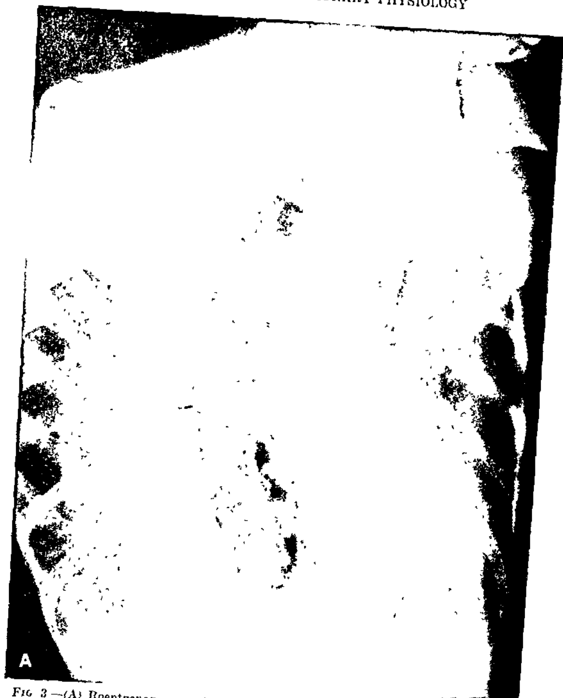


Fig 3 —(*A*) *Roentgenogram*, right anterior oblique projection, of a 55 year old patient (T J) with chronic diffuse *obstructive* emphysema and chronic cor pulmonale. There is a dilated main pulmonary artery trunk, a dilated left pulmonary artery (fleck pulmonale) and forward bulging in the region of the *outflow* tract of the right ventricle encroaching on the retrosternal space

in a clockwise direction about its *longitudinal* axis Such positional changes will often *make* the pulmonary artery segment appear slightly more prominent than usual in both the posterior-anterior projections and the right *anterior* oblique views In borderline cases, therefore, it is sometimes difficult to differentiate this increased prominence due to rotation of the heart from that due to slight dilatation of the pulmonary artery. In pectus excavatum and in fibrotic disease with contraction of the left upper lobe of the lung, bulging of the left middle salient often appears and should also be distinguished from that caused by pulmo-

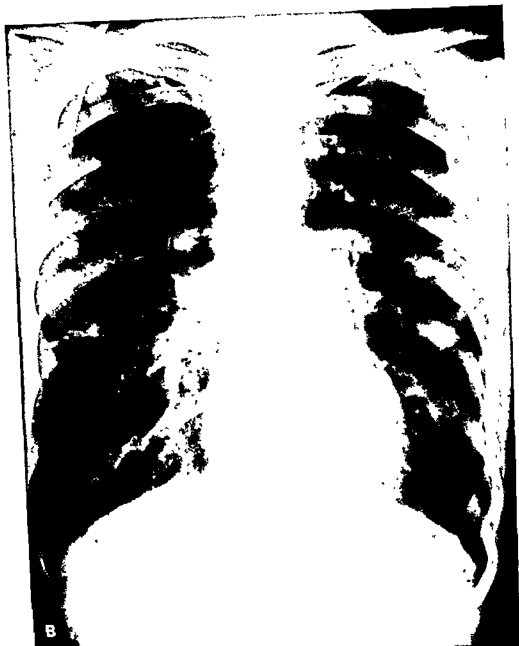


FIG 3 —(B) Roentgenogram, posteranterior projection, of the same patient There is a convexity in the region of the left middle salient (often erroneously called, pulmonary conus) due to dilatation of the main pulmonary artery trunk and the left pulmonary artery Dilatation of the right pulmonary artery is also apparent

nary artery dilatation As the dilatation of the pulmonary artery becomes more marked, it is visible not only in the right anterior oblique position, but can also be recognized in the posterior-anterior projection as an outward convexity of the left middle salient (FIG 3B) Hilar dance is usually not present; this phenomenon usually reflects a greater increase in pulmonary blood flow than occurs in chronic cor pulmonale Calcified atheromatous plaques in the large pulmonary arteries may sometimes also be evident.

Right ventricular enlargement usually is first seen in the right anterior oblique and lateral projections as an anterior bulging in the region of the outflow tract or pulmonary conus of the

right ventricle, encroaching on the retrosternal space (Fig 3A) It should be *noted that by the* time the enlargement of the right *ventricle* is demonstrable in x-rays, dilatation is already *present*; hypertrophy of the free wall of the right ventricle alone cannot be detected roentgenologically in chronic cor pulmonale If concomitant marked left ventricular enlargement is present, the detection of associated right ventricular enlargement may be very difficult, because retrosternal encroachment by the enlarged left ventricle may simulate that due to an enlarged right ventricle An increase in the transverse diameter of the heart in the posterior-anterior projection usually appears very late and is due to displacement of the left ventricle, the right ventricle is still anteriorly located and never forms part of the left border of the cardiac silhouette in this view The development of congestive failure will often make apparent a dilated superior vena cava and an enlarged right atrium Except for its occasional use to exclude congenital heart disease or to localize an arteriovenous fistula in the lung, angiocardiography has not been particularly useful in the diagnosis of chronic cor pulmonale

Cardiac Catheterization

Right heart catheterization is the best method for the early detection of pulmonary hypertension While it cannot be recommended as a routine diagnostic procedure, its use in combination with pulmonary and blood gas studies has led to great advances in our understanding of the disturbed physiology in chronic cor pulmonale It sometimes may be useful to rule out the presence of congenital heart disease. While the presence of pulmonary hypertension is not prima facie evidence of right ventricular hypertrophy, for practical purposes, its presence, especially at rest, in a patient with considerable chronic pulmonary disease justifies the assumption that right ventricular hypertrophy has already developed Early, pulmonary artery pressures may be normal at rest, becoming elevated only with exercise Later, pulmonary hypertension is present at rest.

While these patients have pulmonary arterial hypertension, their pulmonary arterial wedge pressure is normal. This differentiates the pulmonary hypertension present in chronic obstructive emphysema from that which may be present in patients with mitral stenosis or left ventricular failure where both the pulmonary arterial wedge and the pulmonary arterial pressures are elevated.[20] Often, in a patient with chronic cor pulmonale in congestive failure with marked pulmonary hypertension and increased cardiac output, repeat catheterization after intense pulmonary and cardiac therapy will show the cardiac output to be normal, and the pulmonary artery pressures normal or nearly normal at rest, becoming elevated only with exercise [42]

Electrocardiography

The electrocardiogram frequently demonstrates alterations earlier than the roentgenologic examination In addition to the usual leads, special precordial leads over the right chest (V_4R, V_5R) give valuable additional information The changes which are most frequently seen in chronic cor pulmonale due to chronic obstructive emphysema are *those* which are not themselves pathognomonic of right ventricular hypertrophy As a result of the overdistended lung and the depressed diaphragm in chronic obstructive emphysema, the heart assumes a more vertical position and is rotated clockwise about its longitudinal axis, sometimes with backward displacement of its apex This is usually manifested in a mainly inverted QRS in aVL and an upright QRS in aVF (sometimes with S waves in all the limb leads), and a shift of the transitional zone over the precordium to the left, with the persistence of S waves in V_5 and V_6 (Fig 4A) Sometimes, the QRS complex will be of the QS type in V_2 and V_3, due to the marked clockwise *rotation of the heart, and may* simulate the residual changes of an old transmural anteroseptal myocardial infarct (Fig. 4A) The QRS complexes may sometimes exhibit low voltage, especially in the precordial leads This may be due to the increased volume of air-containing lung between the heart and chest wall, or due to a positional change in the heart so that *the direction of the* QRS vector becomes perpendicular to the frontal plane All of these changes will often simulate or be exaggerated by the

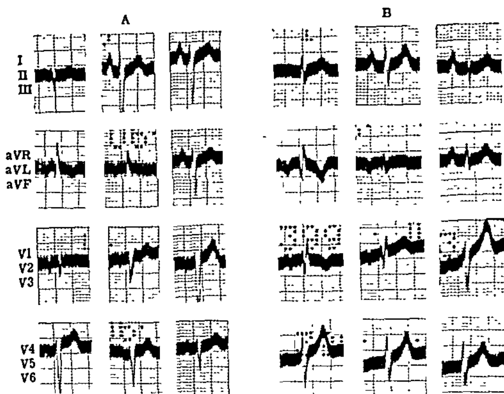


Fig 4—(A) An electrocardiogram of a 65 year old patient (S.M.) with bronchiectasis, chronic diffuse obstructive emphysema and chronic cor pulmonale Sinus rhythm P pulmonale P is inverted in aVR and aVL. An R wave is present in aVR and aVL A deep S wave is present in all limb leads, and in the precordial leads, persisting out to V_6 There is marked shift of the transitional zone over the precordium to the left While there is no definite evidence in this record of right heart strain, the above positional changes with P pulmonale plus the clinical findings justify the presumptive diagnosis of chronic cor pulmonale (B) An electrocardiogram of a 52 year old male patient (F M.) with chronic bronchitis, severe chronic diffuse obstructive emphysema and chronic cor pulmonale Sinus rhythm. P pulmonale P is inverted in aVR and

nale is present

presence of right ventricular hypertrophy or dilatation, since right ventricular enlargement will produce the same kind of rotation of the heart as the pulmonary changes associated with chronic emphysema [104] When, in a patient with chronic obstructive emphysema, P pulmonale is present with these changes, the diagnosis of chronic cor pulmonale becomes extremely likely even though these changes per se are not the result of hypertrophy of the right ventricle

P pulmonale[59] is a tall peaked P wave in Leads 2, 3 and aVF. Usually it is also seen to be small in Lead 1, inverted in aVL, and often diphasic (plus-minus) in V_1 and V_2. It is often associated with depression of the P-Q segment *due to the prominent negative T_P waves* This is apparently a secondary T wave change since it is associated with a high voltage upright P wave. In some patients, it may revert to normal on treatment. The exact mechanism for its production is unknown. While in some cases it may be associated with hypertrophy or dilatation of the right atrium, it frequently is present when these are absent In most cases, it is probably due to positional change; in a vertical heart with a low diaphragm, the apex is displaced in such a way that higher upright P wave potentials ordinarily facing towards the back or other parts are now directed to the feet. P

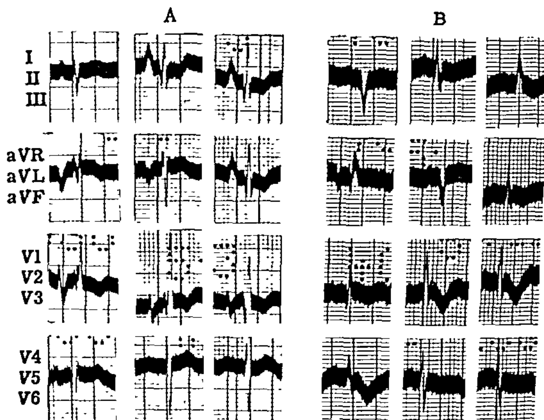


FIG 5 —(A) An electrocardiogram of a 37 year old male patient (B H) with chronic bronchitis, severe chronic diffuse obstructive emphysema, and chronic cor pulmonale Sinus rhythm P pulmonale S-T is slightly depressed in 2, 3 and aVF T is inverted in 3 and aVF P is inverted in aVR and aVL A large diphasic P wave (plus-minus) is present in V_1 and V_2 A tall R′ is present in V_1 through V_3 S-T is slightly depressed and T inverted in V_1 through V_3 Deep S persists to V_6 Electric position is vertical There is a shift of the transitional zone over the precordium to the left This is a definite right ventricular hypertrophy pattern (B) An electrocardiogram of a 40 year old female patient (M K) with metastatic endolymphatic carcinomatosis of the lungs and chr[illegible] and inverted in 2, 3 and aVF [illegible] V_4, and isoelectric in V_5 and [illegible] here is shift of the transitional zone over the precordium to the left This is a definite right ventricular hypertrophy pattern

pulmonale is present in FIGURES 4A AND B, 5A, AND 6A

It has been reported in normal subjects that complexes with secondary R waves (r′) are found in V_4R in about 50 per cent of cases If more right-sided leads are taken (V_5R, V_3R, and an interspace above and below as well) more than 50 per cent show an r′ These are especially frequent when the leads are placed one interspace below However, in normal individuals the S wave usually is seen to be larger than either R deflection, and usually the r′ is smaller than the R [12] Probably the r′ represents activation of the conus of the right ventricle, since it has been known for some time that the conus of the right ventricle and the posterobasal portion of the left ventricle are the last parts of the myocardium to be activated Nevertheless, the appearance of an M-shaped QRS complex (rsR′), with R *taller* than r, in leads over the right precordium (V_4R, V_1 and V_2), which had been called incomplete right bundle-branch system block by some, is usually good evidence of right ventricular strain and hence chronic cor pulmonale (FIG 4B) In some cases, complete right bundle-branch system block with QRS duration longer than 0 12 second may also result from right ventricular involvement in chronic cor pulmonale

The presence of a typical right ventricular

hypertrophy pattern (a relatively tall late R in V_4R or V_1) is usually definite evidence of chronic cor pulmonale (FIG. 5A AND B). An R wave in aVR is not sufficient. The tall R may sometimes be preceded by a tiny Q wave (FIG. 5B). The first type of right ventricular enlargement pattern rsR′ over the right precordium) occurs somewhat more frequently in chronic cor pulmonale due to chronic obstructive emphysema, and the second type (tall late R over the right precordium) occurs more often in chronic cor pulmonale due to pulmonary disease with predominant vascular involvement.[53]

Electrocardiographic changes suggestive and those definite for right heart hypertrophy occur in chronic cor pulmonale only when the hypertrophy is marked. When electrocardiographic evidence of right ventricular hypertrophy is present, it is almost always found at necropsy, but in the majority of cases, particularly when the hypertrophy is slight or moderate, no definite right ventricular hypertrophy pattern is seen in the electrocardiogram We as yet do not understand all of the reasons for the electrocardiographic changes in right ventricular hypertrophy While positional changes are important in influencing the contour, they are certainly not the sole reason The mechanism by which an acute increase in work of the right ventricle, usually associated with dilatation of the chamber, produces the so-called "strain pattern" is also not understood. Furthermore, it is fairly certain that such leads as V_5R, V_4R, and V_1 are remote rather than semidirect leads as was once supposed V_4R does not overlay the heart and V_1 is usually over the right atrium; V_1 and certainly V_4R do not merely represent the potential variation of the epicardial surface of the right ventricle but record the sum of the potential variations of the right atrium, right ventricle and those of the rest of the heart. This is so, also, since aVR, which cannot be supposed to be dominated by right ventricular potentials, often shows an R or RS pattern resembling that found in V_4R and V_1.[12]

The spatial vectorcardiogram in some cases may show a typical pattern of right ventricular hypertrophy when the electrocardiogram is equivocal or negative. It may also help differentiate right ventricular hypertrophy from right bundle-branch system block. However, the changes in heart position that are produced by diffuse obstructive emphysema often obscure the pattern of right ventricular hypertrophy in the spatial vectorcardiogram.

Frequently, the presence of a right ventricular strain pattern is associated with the presence of inverted T waves in V_2 through V_4. These often become upright after treatment. The reason for the inversion of these T waves is not fully understood They may be caused by right ventricular dilatation (reflecting merely an increased clockwise rotation of the heart about its longitudinal axis), acute right heart strain or ischemia of the anterior wall of the heart. After successful treatment in some cases, not only do these T waves become upright, but a shift in the transition zone over the precordium to the right and a reduction in size of the S waves in the limb leads and in V_5 and V_6 also occur This may occur without demonstrable change in position of the diaphragm, but the regression of congestive failure has presumably reduced the right ventricular strain and dilatation Such changes are demonstrated in FIGURE 6A AND B. Absence of a prolonged Q-T interval may help rule out anteroseptal infarction when the T waves are inverted over the right precordium, since it has been reported that the Q-T interval is normal in patients with chronic cor pulmonale in the absence of other types of heart disease.[1] In some patients, previous right ventricular dilatation may be deduced from those changes in the electrocardiogram after intensive therapy which are frequently associated with a decrease in size of the right ventricle. With the shrinkage of the right ventricular chamber, the heart rotates in a counterclockwise direction, so that the transition zone shifts to the right, and R waves may appear in V_2 or V_3 where QS waves were formerly present.

PHYSIOLOGIC BASIS FOR THERAPY

It is only recently that a more optimistic outlook for the therapy of chronic cor pulmonale has appeared. Where the chronic cor pulmonale is due to obstructive emphysema so that many of the pathologic and physiologic

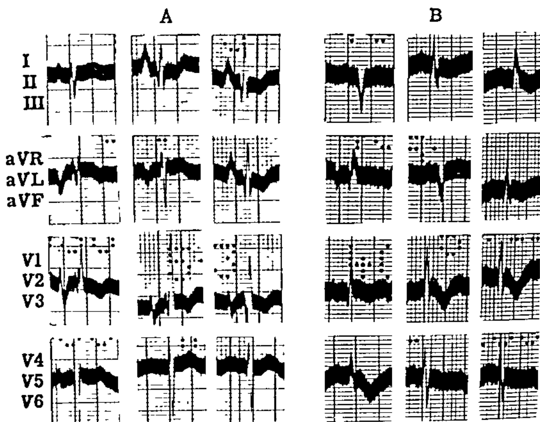


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The presence of a typical right ventricular

blood gas abnormalities, they frequently herald impending pulmonary and circulatory breakdown.[31, 42] These may be prevented by intense therapy.

In active treatment, a vigorous assault on the bronchopulmonary disease is probably more important than specific cardiac measures.[63] The congestive heart failure will respond to therapy only if many of the functional and anatomic abnormalities described above under pathogenesis are at least partially reversed. Increase in the size of the pulmonary vascular bed and alleviation of the hypoxia are thus the main objectives of therapy. This is accomplished by combatting infection, producing an adequate airway, and improving effective alveolar ventilation. These goals are interdependent so that the measures employed have multiple effects. Therapy will include the use of appropriate antibiotics, bronchodilators (orally and parenterally), sputum liquifiers (expectorants and inhalation of aerosols), correction of dehydration, facilitation of cough and expectoration and, when necessary, bronchial aspiration by catheter and bronchoscopy.[90] A tracheostomy may be life-saving, and in some instances will become permanent. Breathing exercises with special training in the effective use of the diaphragm have been helpful in improving pulmonary ventilation. In desperate cases, the use of adrenal corticosteroids will be very valuable, if their potential disadvantages are recognized.

The respiratory center in these patients is usually nonresponsive to either increased partial pressure of carbon dioxide or increased hydrogen ion concentration in the arterial blood, apparently due to a selective depression of the respiratory center to these stimuli. If the hypercapnia has been of long duration, this poor ventilatory response to the carbon dioxide stimulus is usually not reversible, even though the partial pressure of carbon dioxide and the alkali reserve in the arterial blood is restored to normal levels.[6, 32] Yet, the respiratory center still responds to afferent stimuli from special receptors in the muscles since exercise still causes increased ventilation.[32] It is also still responsive to afferent stimuli from the carotid and aortic bodies so that the tachypnea which is necessary in these patients is often maintained mainly by some degree of hypoxemia. The use of pure oxygen consistently depresses the ventilation, thus having a different effect than when given in concentrations sufficient merely to correct the hypoxemia towards the physiologic range.[32, 90] The use of 100 per cent oxygen may thus lead to hypoventilation with carbon dioxide retention, acidosis and death. Nevertheless, because of the disastrous consequences of severe hypoxemia the administration of oxygen is frequently mandatory. It should then be given in lower concentrations, intermittently, well humidified and only if the patient is under constant observation by a physician. Control of the oxygen therapy will depend on its observed effect on the frequency and depth of respiration, the clinical appearance of the patient, and finally, wherever possible, by serial determinations of the arterial blood gases. The latter technics are important since the clinical appearance of the patient may be deceptive. It is often advisable to use oxygen with some type of mechanical respiratory aid such as an intermittent positive pressure breathing device or a tank type body respirator to hyperventilate the patient in an attempt to "wash out" retained carbon dioxide at the same time that oxygen is being administered,[7] this may have to be continued over a period of several weeks, since the carbon dioxide stores in the body are not confined to the blood alone but include also those present in all the body fluids and fat. Respiratory depressants such as morphine are strongly contraindicated.

Acetazoleamide (Diamox), a carbonic anhydrase inhibitor, has proven useful in the treatment of patients with chronic cor pulmonale and hypercapnia, with or without congestive failure. Diamox has been observed to decrease the alkali reserve (plasma bicarbonate) and the partial pressure of carbon dioxide in the arterial blood. The former effect depends on its action in promoting the excretion of bicarbonate and the bicarbonate bound base by the kidney, the latter probably to an improvement in alveolar ventilation, possibly by increasing the response of the respiratory center to the carbon dioxide stimulus.[37, 57] Diamox also frequently acts as a mild diuretic, being much more efficient in the congestive failure of chronic cor pulmonale than

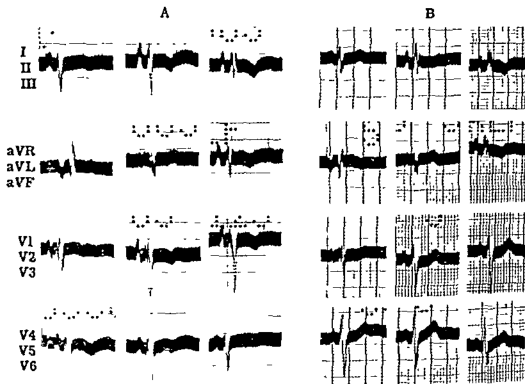


FIG 6 —Electrocardiograms of a 50 year old male patient (J C) with chronic bronchitis, severe chronic diffuse obstructive emphysema and chronic cor pulmonale (A) In severe pulmonary insufficiency, with secondary polycythemia and congestive heart failure following an acute respiratory infection Sinus rhythm P pulmonale A deep S wave is present in all limb leads and in aVF T is inverted in 2, 3 and aVF A tall R preceded by a tiny Q is present in aVR In V_1 and V_2 the QRS complex demonstrates rsR'S' T is inverted in V_1 through V_5. T is flattened in V_6 There is marked shift of the transitional zone over the precordium to the left (B) An electrocardiogram taken five months later, after intensive pulmonary and cardiac therapy Sinus rhythm P
3 and aVF R is now small
T is now upright in all the
to the record shown in A, there has been marked shift of the transitional zone over the precordium to the right These changes are a result of a reduction in strain on the right ventricle and decrease in its size, with resultant counterclockwise rotation of the heart about its longitudinal axis

changes are partially reversible, substantial improvement will frequently result from treatment. Where the chronic cor pulmonale is secondary to a pathologic process localized mainly in or about the pulmonary vessels, the outlook for treatment is less favorable The pessimistic attitude in the past arose from a failure to differentiate among the various causes of chronic cor pulmonale, the imperfect understanding of the pathologic physiology of chronic cor pulmonale and the failure to separate the symptoms due to the pulmonary disease from those due to cardiac failure. Moreover, the newer technics in the treatment of bronchopulmonary disease were not available.

Treatment of Cor Pulmonale Due to Chronic Obstructive Emphysema

With the specter of chronic cor pulmonale before us, the importance of prophylaxis becomes self evident Chronic bronchitis must be attacked vigorously, not only by a studied medical regime but also by corrective manipulation of the environment This includes attention to industrial safeguards, air pollution poverty and health education In patients with diffuse obstructive emphysema, acute respiratory infections should be treated as major illnesses. Their effects may not only be cumulative and lasting, but with signs of increasing pulmonary dysfunction, polycythemia and

pathology tends to be localized in or about the pulmonary vessels, therapy is much less satisfactory. Harvey and associates have advised continuous marked restriction of physical activity in these patients as one of the few procedures which can be employed to reduce the strain on the right heart, since the pulmonary vascular bed is restricted in a permanent anatomical manner.[42] Associated bronchopulmonary infection and diffuse obstructive emphysema if present should be treated intensively Where there is interstitial infiltration with granulomata which will respond to specific medication, such as the adrenal corticosteroids, these should be employed. However, it is usually impossible to predict whether resolution or fibrous of these granulomata will occur. Patients with multiple recurrent small pulmonary emboli, thrombosis of major pulmonary arteries, or primary pulmonary hypertension should probably be on long-term anticoagulant therapy. With a pulmonary vascular bed which is markedly restricted, great care must be used in the administration of intravenous fluids, since even small injections may cause collapse and death In most of these cases, oxygen in high concentration must be given; there is usually no danger of respiratory depression as would occur in patients with chronic diffuse obstructive emphysema or the chronic alveolar hypoventilation syndromes

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that associated with other types of heart disease Diamox has also been helpful in alleviating the nocturnal headaches which are apparently caused by carbon dioxide retention resulting from the sleeping hypoventilation [63]

While there has been good evidence that salicylates in large doses stimulate respiration,[97] their use in the treatment of the hypercapnia of patients with pulmonary insufficiency has been disappointing Furthermore, in patients with chronic diffuse obstructive emphysema, the stimulation of respiration may be disadvantageous if the work of breathing is increased beyond a critical level so that the augmented work of the respiratory muscles increases carbon dioxide production beyond the capacity of the lungs to eliminate it [84] Far more rational is therapy directed to reduce the work of breathing by the methods listed above, or the use of a mechanical respirator

Patients with chronic cor pulmonale in congestive failure and respiratory acidosis are critically ill. They are often very difficult to manage As a result of hypoxia and hypercapnia they are frequently somnolent, confused and uncooperative Cerebrospinal fluid pressure is often increased, even to the extent of producing papilledema [34] [80] Only the most diligent care and minute attention to detail will restore the patient to an alert state where co-operation with therapeutic procedures and more effective coughing can result

Cardiac therapy will be effective, only if combined with the above pulmonary measures Digitalis, contrary to earlier reports, has been shown definitely to improve cardiac performance in patients with chronic cor pulmonale and congestive failure,[30] and is therefore indicated Mercurial diuretics and salt restriction should also be employed, but the development of electrolyte imbalance should be avoided. Restriction of physical activity particularly during the period of pulmonary and circulatory insufficiency is extremely important in order to reduce the body's metabolic requirements Phlebotomy becomes important in the presence of polycythemia. The possible advantages and disadvantages of polycythemia and of the asso-

themia are often hypochromic, consideration should be given to the hemoglobin as well as to the red blood cell counts and hematocrit Bleeding is advisable when the hematocrit is above 55, 300 to 500 cc of blood may be removed every three to five days to bring the hematocrit down to 50, and the hemoglobin to about 14 Gm Since many of these patients have associated arteriosclerotic or hypertensive heart disease, the presence of some degree of left ventricular failure due to these associated conditions will often result in a particularly gratifying response to specific cardiac therapy Thyroid ablation with radioactive iodine to lower the basal oxygen requirements of the body has proven less useful than expected [45] Surgical excision of giant bullae has been of value in selected cases.

Peptic ulcer has been noted to occur with much greater frequency in patients with chronic obstructive emphysema than in the general population [36] [63] Barium studies of the upper gastrointestinal tract should therefore be done routinely, these are particularly important if corticotropin or adrenal corticosteroid therapy is to be employed, since these drugs notoriously cause reactivation of peptic ulcer.

Treatment of Cor Pulmonale Due to Chronic Alveolar Hypoventilation Syndromes

Treatment of the chronic alveolar hypoventilation syndromes (Type II) will be futile unless concomitant improvement of alveolar ventilation is achieved. An acute respiratory infection is often a lethal complication with the production of severe hypoxemia, hypercapnia and right heart failure At such a time, all the measures described in the treatment of severe obstructive emphysema are necessary Relief of the hypoxemia lifts much of the burden from the heart Abolition of the hypercapnia may restore the sensitivity of the respiratory center to the carbon dioxide stimulus Where alveolar hypoventilation is associated with obesity, weight reduction has often been most effective in reversing the pulmonary and cardiac dysfunction.

Treatment of Cor Pulmonale Due to Pulmonary Disease with Predominant Vascular Involvement

Where the chronic cor pulmonale is of the third type, due to pulmonary disease where the

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Functional Disturbances Simulating Cardiopulmonary Disease

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A GROUP of symptoms usually associated with disturbances in cardiovascular or respiratory function but unassociated with structural heart or lung disease has long been recognized as both a clinical reality and a pathophysiologic puzzle Broadbent in 1898[1] clearly recognized this problem in the introduction to his chapter, "Functional Affections (so-called) of the Heart": "The term 'functional affections' is retained not for any merit of its own but for want of a better one. Under it must be discussed a variety of symptoms having the heart for their centre, but which cannot be assigned to any structural change "

Many names have been applied to these disturbances including: "cardiac neurosis," "neurocirculatory asthenia," "effort syndrome" and "disordered action of the heart." The principal symptoms are: (1) dyspnea, often associated with sighing respiration, (2) palpitation, (3) chest pain, (4) easy fatigue and (5) dizziness and syncope.

These symptoms will be discussed individually from the standpoint of the physiologic abnormalities, clinical recognition and management.

Dyspnea

Under certain conditions of acute or chronic emotional tension or anxiety the normal autonomic and chemical control of the rate and depth of breathing may be disturbed with resulting hyperpnea or hyperventilation. Although this may resemble the dyspnea of cardiac failure, it usually may be differentiated by the patient's excessive awareness of the act of breathing, by the frequent sighing respiration, by the intermittent nature of the breathlessness, the associated dizziness and faintness and the poor relationship between the breathlessness and the degree of exertion.

The symptom of dyspnea, simulating ventilatory insufficiency, occurring most frequently in women, is caused by nervous overstimulation of the respiratory center in the presence of emotional stress or tension. It is characterized chiefly as a subjective complaint of "sighing" respiration—the inability to "get enough air in " In the mild form, "shortness of breath" is the only complaint, with all physical and chemical tests normal. The more severe, with or without consciousness of dyspnea, is known as "hyperventilation syndrome."[9, 10] The aroused sympathetic nervous system stimulates the cerebral cortical centers and the adrenals, causing rapid heart action and increased respiration. With increased ventilation the carbon dioxide in the alveolar spaces is expelled; more is shifted from the blood stream and tissues into the alveolar spaces, with resulting alkalosis. This, in turn, may reduce the ionized calcium in the blood which increases the excitability of peripheral sensory nerves. This results in constriction of the throat, giddiness, circumoral numbness, paresthesias and stiffness of the fingers and toes, slight nausea, weakness and easy fatigability. For diagnosis, the symptoms usually can be reproduced by having the patient hyperventilate for three minutes, preferably in the sitting position

The treatment for either the mild or more severe forms of functional dyspnea requires the elimination of all contributing organic causes, with a careful appraisal of the emotional situa-

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determine whether one or another of these agents is an important cause of the palpitation

In the absence of organic heart disease, the treatment for palpitation calls for reassurance and proper sedation In mild cases, with infrequent attacks, reassurance may be sufficient. The barbiturates, chloral hydrate or the newer phenothiazine derivatives may be used. In mild cases, the Rauwolfia derivatives are sometimes helpful. Any underlying factor, such as hyperthyroidism and anemia, should be corrected

Chest Pain

Chest discomfort of a disturbing or painful nature occurs commonly in patients with functional cardiovascular disturbances as well as in patients with organic heart disease. Both types of discomfort may coexist.

The physiologic transmission of pain impulses from the skin, chest wall, pleural surfaces, mediastinal structures other than the heart and blood vessels and skeletal structures of the chest passes over the afferent sensory pathways of the intercostal nerves Trauma, tissue tension, infections or chemical irritants and pressure on these nerves may cause pain. Prolonged psychic tension or anxiety states may set up skeletal or smooth muscle tension or increased tonicity which in time are perceived as painful sensations

The cardiac-aortic pain fibers arising in the cardiac and aortic plexuses pass through the sympathetic trunk and the rami communicantes to the dorsal root ganglia Some fibers enter the middle cervical ganglion, passing inferiorly through the sympathetic trunk to the stellate ganglion and on to the corresponding spinal roots Some few fibers may go through the superior cervical ganglion to the trigeminal ganglion.

The prototype of functional chest pain is that noted in neurocirculatory asthenia, or effort syndrome. The distress usually is described as sharp, lancinating, stabbing, a "stitch" of momentary duration or as a "dull ache" or "tired feeling" that may last for hours or days, with tender skin over the precordium, apex or left anterior chest. Such psychogenic pain occurs after exertion or excitement It is not relieved by nitroglycerine, as in angina pectoris Similar pain occurs with the anterior chest wall syndrome,[8] noted in coronary thrombosis, but it may occur also in normal, healthy individuals. It should be mentioned that the pain of both neurocirculatory asthenia and the chest wall syndrome may occur as a psychogenic symptom in patients with organic heart disease as well.

The differential diagnoses include angina pectoris, coronary thrombosis, referred pain of cervical or thoracic spondylitis, esophageal hiatus hernia, pulmonary embolism, dissecting aneurysm of the aorta, pericarditis, rheumatic heart disease with the pain of pulmonary hypertension, and spontaneous pneumothorax. With symptoms of anxiety, palpitation, dyspnea, sweating and fatigue, it is important to exclude thyrotoxicosis, tuberculosis, hypoglycemia, recent severe anemia and undulant fever and other forms of low-grade fever.

Treatment includes reassurance of the patient, with psychotherapy and rehabilitation. The basic studies should be repeated in persistent cases

Easy Fatigue

One of the most common complaints in patients with functional cardiovascular disturbances is that they "tire easily" particularly when attempting to perform hard work In some patients, there is a feeling of exhaustion, noticeable on awakening in the morning Still others find that after a period of tension or anxiety, they are weak, giddy and even faint.

Although the physiologic explanation of this easy fatigue is quite incomplete, there is suggestive evidence that these patients have certain basic metabolic abnormalities. Not only are these patients unable to sustain steady treadmill or step-up exercise for a normal period,[6] but their blood lactate concentrations are 2½ times as high with the same exercise as in normal subjects [3] These patients on occasion, may have a low tidal air at rest,[4] a remarkable sensitivity to increases in inspired CO_2,[7] and an increase in palmar sweat.[2] Oxygen consumption during exercise is low, with the development of a high oxygen debt. This, together with the

tion of the patient The patient should be instructed to hold the breath when the sensation of dyspnea occurs This may be effective. Next in importance is the use of mild to moderate sedation to help break the vicious cycle. For this, the barbiturates, chloral hydrate, or the new tranquilizing drugs may be used Acid salts, such as ammonium chloride, 3.0 Gm. per day, are useful to maintain a mild state of acidosis so that hyperventilation alkalosis may not become manifest as readily Such measures as an acid-ash diet and limitation of fluids are of limited value

Palpitation

Palpitation is characterized as an unpleasant or unusual awareness of the heart's action It is usually associated with some change in the rate, rhythm, or force of the heart beat Even in definite heart disease palpitation may not be experienced without a change in rate or rhythm In the normal heart, palpitation may be produced by effort, excitement, infections or such toxins as tobacco, caffeine and alcohol

Palpitation is not uncommon in individuals who are emotionally tense or nervously exhausted and suggests a functional rather than organic disturbance, but it may occur in the presence of actual heart disease with disorder of rate or rhythm In either case, the transmission of the abnormal sensations and reactions is through the autonomic nervous system. Resulting imbalances in the vagus and the sympathetic nerves cause palpitation and tachycardia or bradycardia

Afferent vagal fibers arise in the inflow and outflow tracts of the heart and the carotid sinuses and set up reflexes through the medullary cardiac centers, sending out efferent impulses to the heart and blood vessels The vasodilator and vasoconstrictor system and cardio-accelerator and cardio-inhibitory centers are the source of these reflex arcs They may be influenced by any of the afferent sensory nerves of the body and apparently become more sensitive in tension or diseased states.

The action of the vagus nerve is primarily a slowing or depressor effect on the heart rate, tending to counterbalance the normal somewhat inherent rhythmicity of the heart muscle. Contrarily, the sympathetic nerves tend to accelerate the action of the heart. Anxiety and stress-producing situations may cause increased sympathetic activity and increased elaboration of epinephrine and norepinephrine. These, in turn, will result in acceleration of the heart, and elevations of the cardiac output and blood pressure These physiologic changes may result in palpitation whether associated with a normal heart or with organic heart disease.

In many instances, palpitation results from a disturbed cardiac rhythm, often secondary to organic heart disease. Premature contractions or extrasystoles constitute one of the commonly encountered arrhythmias which may cause palpitation and considerable anxiety. When extrasystoles persist or become worse with exercise, the likelihood of organic heart disease is much greater than in certain patients in whom extrasystoles disappear with exercise.

It is known that chemical control of the heart beat can be obtained by certain ions such as sodium, which must be present in proper concentration in blood plasma in order for the heart muscle to function properly Potassium ions are somewhat depressing to heart muscle and favor the relaxation phase of the heart cycle Calcium ions increase contractility of heart muscle and increase the duration of systole

Disturbances of heart rate, or rhythm, can be recognized by careful examination at the bedside However, they should be studied graphically for critical evaluation with electrocardiography or the vectorcardiogram In addition, there should be a careful survey of the drugs the patient is taking, with a review of blood electrolytes Studies of thyroid function must not be overlooked It should be emphasized that almost all of the arrhythmias can occur at times in patients with no organic heart disease

Attempts should be made to produce palpitation by observing the patient in many positions or by having him bend over or perform exercise. The effects of excessive smoking, caffeine or alcohol should be observed individually to

and syncope. Any of these may simulate heart disease or a "heart attack" Individuals who are constitutionally predisposed to develop manifestations may be sensitized by situations of stress, anxiety, exhaustion, toxins or infections, and the resulting symptoms may become magnified It should be emphasized that physical incapacity may occur, even in the absence of organic heart disease.

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high blood lactate concentration, suggests poor aerobic and increased anerobic metabolism [5]

The interpretation of a symptom such as easy fatigue requires exclusion not only of organic heart disease (particularly aortic stenosis, constrictive pericarditis or certain arrhythmias) but also of such conditions as adrenal cortical insufficiency, hypothyroidism or hyperthyroidism, chronic pulmonary insufficiency, anemia, neoplastic disease, chronic infection or chronic hypoventilation

If organic disease is not present, reassurance is most important particularly to allay the patient's fears of organic disease The patient should be advised to resume moderate activity and to obtain adequate food and sleep If the patient is obese, weight reduction should be recommended Finally, some of these patients obtain distinct symptomatic benefit from some of the newer psychotherapeutic drugs particularly some of the newer phenothiazine compounds.

Dizziness and Syncope

Slightly less common symptoms among the functional cardiovascular disturbances are dizziness and syncope. Dizziness or giddiness most often occurs following the anxiety associated with dyspnea, palpitation or chest pain In many instances, dizziness is the result of hyperventilation with lowering of the alveolar (and arterial) CO_2 tension with resulting alkalosis. There may be associated muscle cramps, tremor, and even early tetany If the hyperventilation persists, syncope, a sudden loss of consciousness of short duration, may ensue If these symptoms are the result of hyperventilation, the patient should be instructed to hold his breath or to breathe into a paper bag when he first experiences these symptoms Many other causes of dizziness and particularly syncope must be considered These include orthostatic hypotension (see Chapter 12), carotid sinus syndrome (see Chapter 18), anoxic syncope (high altitudes), tussive syncope, epilepsy, hypoglycemia, Meniere's disease, alterations in cardiac rhythm including Stokes-Adams syncope (see Chapter 18), aortic valvular stenosis (see Chapter 14) and finally "vasovagal" syncope or simple fainting.

Syncope may simulate a "stroke" or a "heart attack." Most often syncope is associated with nervous or vascular influences, without cardiovascular pathology, but it can and does occur in patients with organic heart disease Syncope differs from "shock," in which the unconsciousness is prolonged. Furthermore, shock and coma occur more frequently in diseased states

In the usual case of syncope of circulatory origin, there occurs a disproportion between the total blood volume and the total vascular volume, which is accompanied by a reduction of the circulating blood volume The result is a decreased return of blood to the right side of the heart, hence a diminished circulating ("effective") blood volume, a decreased cardiac output, lowered arterial and capillary pressures and, finally, anoxia of certain tissues, particularly of the brain

The diagnosis of the various types of syncope, as discussed, usually can be made with a detailed history of symptoms and events before, during and after such an attack, and by a careful physical examination. Special tests may be required, such as a blood count for anemia, blood sugar, carotid sinus stimulation, electrocardiography and electroencephalography. Drugs as a cause of the phenomenon must always be excluded.

Treatment should begin with the recumbent or head-down position, and loosening of all tight clothing. Stimulants such as aromatic spirits of ammonia may be used, but alcohol, because of its vasodilating effect, should be avoided For postural hypotension, any large varicose veins should be treated, adrenocortical insufficiency should be ruled out Such drugs as Isuprel, ephedrine sulfate, paredrine hydrobromide and Neosynephrine may be helpful. For carotid sinus sensitivity, the sympathomimetic drugs with the addition of tincture of belladonna or atropine sulfate are useful Surgical denervation of the carotid sinus may be necessary

In summary, it should be mentioned that these various physiologic disturbances may be associated with the sensory nervous system, autonomic regulatory mechanism and hormonal control of the heart. They may produce symptoms of dyspnea, palpitation, disturbances of *cardiac rate and rhythm, chest pain*, dizziness

1. Manual methods of artificial respiration.
2. Expired air ventilation.
3. Mechanical methods

Manual Methods of Artificial Respiration

The main principle involved is the application of external positive pressure on the respiratory framework for the expiratory phase and subsequent passive inhalation. There are some modifications in which the inspiratory phase may be aided by a part of the manuever, e.g., the Holger-Nielsen method, which consists of two phases—an arm-lift and a back-pressure. The arm-lift phase augments inspiration whereas the back-pressure phase provides positive pressure exhalation. The Sylvester method, which consists of lifting the arms above the head (the patient is in the supine position) and then bringing them down to the sides and compressing the thorax at the same time, falls into the same category as the Holger-Nielsen. The other methods such as the Schaefer method, the hip-roll method, the hip-lift method, the Eve rocking-bed method all are dependent on application of positive pressure on the expiratory phase. The positive pressure may be applied directly on the thorax (Schaefer) or may depend on intra-abdominal viscera pushing the diaphragm cephalad to expel air. The hip-lift, the hip-roll and the rocking-bed methods are of the latter type. With the Eve rocking-bed method, however, as the bed slants down towards the feet, the caudad migration of the abdominal viscera draws the diaphragm in the same direction and augments inspiration.

The efficacy of the manual methods of artificial respiration were evaluated by Gordon[12] and his associates at the University of Illinois on volunteers. Their findings point to the arm-lift-back-pressure method (Holger-Nielsen) as the most efficient and convenient in terms of both the victim and the rescuer. It was not taxing to the rescuer and provided sufficient amounts of air for the victim. In fact, this method was subsequently recommended and adopted universally for artificial respiration. However, certain drawbacks developed. It was not realized at the time of evaluation, that the conditions under which these methods were tested were ideal, i.e., (1) all the subjects were completely paralyzed and (2) all the subjects were provided with an almost ideal airway—the endotracheal tube. Under these conditions, compliance was excellent, and the airway remained assuredly patent. Unfortunately, when these methods were re-evaluated without the endotracheal tube and without the flaccid paralysis provided by curare, manual artificial respiration proved inadequate in the unconscious subject. It was observed that upper airway obstruction developed frequently and compliance was poor, so that the efficiency of the method diminished greatly. However, before relegating these methods into obscurity, one must state that they still have a place in situations in which the rescuer may not be familiar with other methods of performing artificial respiration.

Expired Air Ventilation (Fig. 1)

This term was adopted as the correct and inclusive title for mouth-to-mouth breathing and all its modifications. The principle involves the application of positive pressure directly into the airway to provide the inspiratory phase of ventilation. Exhalation is passive. It does approximate normal ventilation more than the manual method of artificial respiration. Modifications of mouth-to-mouth breathing are: (a) mouth-to-nose, (b) mouth-to-mask, (c) mouth-to-oropharyngeal airway, (d) mouth-to-endotracheal tube, and (3) combinations of these technics. This age-old method of artificial respiration may be repugnant to the fastidious, but modifications have diminished the intimacy associated with direct mouth-to-mouth breathing and its efficiency has been tested and proved.

The fact that expired air discarded by one individual is used to ventilate another individual immediately provokes the question of whether or not the method is physiologic. The evaluation of the effectiveness of this technic has, therefore, been oriented along three main factors: (1) the oxygenation of both victim and rescuer, (2) the carbon dioxide concentration in both victim and rescuer and (3) the physical ability of the rescuer to ventilate the subject for prolonged periods of time under easy or difficult situations, e.g., poor compliance of

Resuscitation: Asphyxia and Cardiac Arrest

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IN recent years, a greater appreciation of the pathophysiology of certain cardiovascular and pulmonary diseases has been accompanied by improved therapy for many of these disturbances. The improvements in methods of resuscitation have resulted both from the basic understanding of the physiology of these disturbances and from advances which have made new technics and equipment available for use in resuscitation

As a result, an alert and well equipped medical emergency unit now may often carry out effectively resuscitative measures which were not even contemplated 20 years ago It is becoming increasingly important that physicians everywhere become more familiar with modern methods of emergency resuscitation.

The two functions necessary to sustain life (on a minute to minute basis) are respiration and circulation Resuscitation, therefore, involves primarily restoring the function of respiratory and/or the cardiovascular systems so as to supply oxygen to and remove carbon dioxide from body cells, particularly those of the central nervous system

Resuscitative measures therefore must be directed toward maintaining (1) ventilation, (2) alveolar-capillary gas exchange and (3) blood flow, both systemic and pulmonary

Ventilatory failure from whatever cause results in asphyxia, the combination of hypoxia and hypercarbia The causes of ventilatory failure include: (a) paralysis of the muscles of respiration, either from drugs with a curare-like action, from diseases such as poliomyelitis, myasthenia gravis or muscular dystrophy, or from a severe injury to the central nervous system; (b) extensive injury to the bony framework of the thorax; (c) hemothorax; (d) pneumothorax; and (e) obstruction of the respiratory passages (tracheobronchial tree, larynx or pharynx).

Failure of alveolar-capillary gas exchange may occur acutely as a result of pulmonary emboli, pneumonia or pulmonary edema Slower development of this failure may be associated with other disturbances of the lungs. pneumoconioses, atelectasis or pulmonary fibrosis. This type of failure results primarily in hypoxia and less frequently requires full-scale resuscitative measures

Respiratory failure thus may be sudden and acute or may develop slowly over a period of time Whatever the mode of onset and whatever the type, whether it is a ventilatory failure or an alveolar-capillary exchange failure, oxygen deficiency develops, and the central nervous system suffers since it is most vulnerable to hypoxia In view of this vulnerability, it becomes mandatory that immediate efforts be instituted to take over or augment the lost function This may mean artificial respiration, simple ventilatory assistance, or improving alveolar-capillary gas exchange.

Management of Respiratory Failure

Sudden ventilatory failure is not as serious and dangerous to life as is frequently imagined provided means for resuscitating the patient are available, the principles of resuscitation are known and procrastination is avoided Whatever the method of resuscitation employed, certain principles must be adhered to:

1 A patent airway must be maintained.

2. Enough air must be supplied to the victim such that the total amount per minute will approximate his normal minute volume.

3 There must be efficient elimination of carbon dioxide

4 Cardiovascular function must be sufficient to transport the oxygen to the brain.

Methods of Artificial Respiration

There are three main systems or methods for providing artificial respiration and augmenting diminished respiration:

1. Manual methods of artificial respiration
2. Expired air ventilation.
3. Mechanical methods

Manual Methods of Artificial Respiration

The main principle involved is the application of external positive pressure on the respiratory framework for the expiratory phase and subsequent passive inhalation. There are some modifications in which the inspiratory phase may be aided by a part of the manuever, e.g., the Holger-Nielsen method, which consists of two phases—an arm-lift and a back-pressure. The arm-lift phase augments inspiration whereas the back-pressure phase provides positive pressure exhalation. The Sylvester method, which consists of lifting the arms above the head (the patient is in the supine position) and then bringing them down to the sides and compressing the thorax at the same time, falls into the same category as the Holger-Nielsen. The other methods such as the Schaefer method, the hip-roll method, the hip-lift method, the Eve rocking-bed method all are dependent on application of positive pressure on the expiratory phase. The positive pressure may be applied directly on the thorax (Schaefer) or may depend on intra-abdominal viscera pushing the diaphragm cephalad to expel air. The hip-lift, the hip-roll and the rocking-bed methods are of the latter type. With the Eve rocking-bed method, however, as the bed slants down towards the feet, the caudad migration of the abdominal viscera draws the diaphragm in the same direction and augments inspiration.

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FIG 1 —Expired air ventilation (mouth to-mouth breathing, rescue breathing) (A) Demonstration of the positioning of the patient with the chin grasped between the right thumb and fingers so that the angle of the jaw may be pulled forward and the tongue held down by the thumb The nose is closed by pinching it between the left thumb and forefinger The rescuer's mouth is opened wide so as to cover the victim's mouth as the rescuer insufflates the victim's lungs (B) Exhalation after mouth-to-mouth inflation At this time the rescuer observes the degree of rise and fall of the chest in order to determine whether adequate ventilation is being achieved (C) Mouth-to-mask breathing (D) Mouth-to-airway breathing with use of the Safar oropharyngeal airway

victim's chest. Oxygenation was found to be more than adequate If the adult rescuer ventilates the victim 20 times per minute with a tidal exchange of 500 ml., this would amount to 10 L. or 10,000 ml per minute. Since exhaled air contains an average of 18 per cent oxygen, 1,800 ml of oxygen per minute are available in the expired air for resuscitating the victim. He will require only 300 ml per minute for metabolic purposes; indeed, there is more than sufficient oxygen available in the expired air of the rescuer.

Carbon dioxide which is one of the chief products of metabolism may build up to dangerous levels in the apneic individual leading to hypercarbia and respiratory acidosis with all its pathophysiologic consequences. Since the carbon dioxide concentration in the expired air of the rescuer is 4 to 5 per cent, it might be thought that this exhaled air would increase the hypercarbia Actual determinations in the arterial blood and alveolar air of both rescuer and victim showed carbon dioxide levels to be normal or even lower than normal.

Tests conducted to determine the ability of the rescuer to pursue the course of resuscitation over prolonged periods and under unfavorable conditions (e g, poor compliance) showed no significant fatigue of the rescuer To prevent overventilation, which can lead to dizziness in the rescuer, a rate of 12 to 20 inflations per minute with a tidal volume of about 1,000 ml was recommended.

The technic of oral resuscitation is quite simple:

1 Assure a clear airway by (a) removing any foreign body or material in the oropharynx or trachea and (b) preventing the base of the tongue from falling against the oropharynx by

pushing the lower jaw forward so it assumes the prognathus or the "sniffing air" position.

2. The rescuer's mouth is placed over the nose or mouth of the victim; or if the victim is a child, over the mouth and nose. The rescuer then blows with a smooth steady action until the chest is observed to rise

3 The rescuer removes his mouth from victim's mouth and allows the victim to exhale (Fig. 1B).

4. He continues this technic at a rate of approximately 20 respirations per minute.

In a child, it may be wise to apply a gentle pressure over the abdomen with one hand to prevent stomach distention, which may easily interfere with the victim's breathing and may cause harmful reflexes to the heart.

Various modifications of the mouth-to-mouth breathing may be seen in the accompanying illustrations (Fig. 1C and D).

The use of a face mask has been advocated by Elam and his group[11] The rescuer blows into the face mask instead of coming directly into contact with the patient's mouth. Lee, Tarrow and Ward[15] of the Air Force have modified this mask by attaching a piece of extended tubing provided with a valve through which the victim may exhale after ventilation by the rescuer Safar[21] has introduced the use of a modified Guedel oropharyngeal airway. Two oropharyngeal airways attached together at the mouthpiece (end) serve as a means of breathing into the victim and at the same time providing a patent airway by preventing the tongue from falling back against the pharynx

A recent modification of mouth-to-mouth resuscitation is the "head-tilt" method studied conjointly by several groups of investigators.[12] The essential difference between this method and the technics described above is in the provision of an assured patent airway. This is achieved by tilting the head backwards on the neck at the atlanto-occipital joint as far as is feasible. Although patency of airway may be achieved in many instances with this head-tilt position, it may be difficult in the person who is not relaxed and the individual who is muscular with a short, "bull" neck. It must also be pointed out that in the extremely relaxed subject, dislocation of the cervical vertebrae with damage to the spinal cord is possible. The use of the nose instead of the mouth is advocated in the adult especially when trismus is present and the mouth may not be easily opened This would seem logical except in some individuals who are predominantly mouth breathers and whose nasal airways may not be too patent.

Expired air ventilation with all its modifications serves as a simple effective means of resuscitating a patient. For emergency conditions when an efficient method for artificial respiration is suddenly needed, this technic is unhesitatingly recommended. In retrospect, one must admire the wisdom of some of the age-old methods handed down from antiquity, even if their appreciation of modern physiology may have been minimal

Mechanical Methods of Artificial Respiration

Since most available mechanical units provide positive pressure either to assist deficient ventilation or provide artificial respiration in apnea, these contrivances may be divided into two main groups: (1) those that apply pressure directly to the tracheobronchial tree through a face mask, an endotracheal tube or a tracheostomy tube and (2) those that apply pressure to the thoracic cage, the abdominal wall or both.

Respirators applying pressure directly to the tracheobronchial tree In this group are intermittent positive pressure units and anesthesia respirators:

a First, there are those units that *only* supply positive pressure at regular intermittent intervals. The rates and pressures supplied by these units may be regulated. Pressures may vary from 0 to 60 cm. of water. Originally, most of the units in this category supplied positive pressure on demand. They were primarily assistors. Recently, most have been converted into units also capable of providing artificial respiration automatically. Most or all of these units depend on a valve which regulates the rapid flow of oxygen or oxygen-air mixtures to the mask, endotracheal tube or tracheostomy tube. These valves may be triggered by very small amounts of pressure,

usually the patient's inhalation. When the valve opens, oxygen or oxygen-air mixture is rapidly transmitted to the patient. The pressure governing this stream of oxygen is approximately 50 lbs. per square inch. (Only a small fraction of this pressure passes through the valve to reach the patient.) In most instances, pressures in the mask or airway equivalent to 10 to 20 cm. water are utilized. Outstanding examples of this type of unit are the Bennett IPPB (Fig. 2), the Bird respirator, the Pneophore, the Emerson, the Monaghan and the Dotco. Special mention is made of the Morch respirator, which is also an intermittent positive pressure unit but consists of a big, piston-type pump operated by an electric motor (Fig. 3). The volume delivered by the pump may be regulated to some extent. The rate may be regulated much more accurately. This pump respirator has proved useful in certain types of respiratory failure.

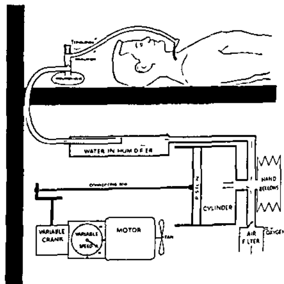


Fig. 3.—Diagram of the Morch Piston Respirator. The various components and the direction of air flow are indicated.

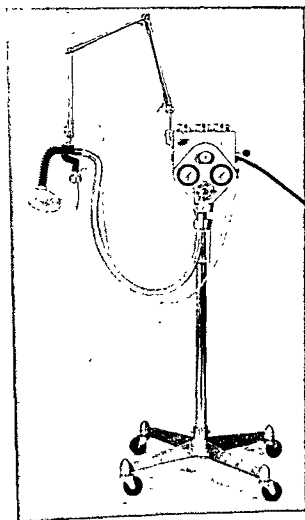


Fig. 2.—Bennett intermittent positive pressure breathing unit and respiratory assistor.

b. Anesthesia respirators of which there are quite a number comprise the second big group falling under the category of intermittent positive pressure units. These are characterized by several factors: (1) They exert pressure on the patient's airway through an anesthesia machine. (2) In addition to positive pressure, they are capable of exerting a negative pressure, and (3) some of the units are capable of either assisting a patient's breathing or providing artificial respiration, and may shift from one category to the other depending on the patient's breathing efforts. These units utilize the principle which depends on the limitation of volume of gas delivered to the patient, on the amount of pressure exerted on the patient's airway or a combination of both. The application of a negative pressure minimizes much of the deleterious effect exerted on the heart and great vessels by positive pressure especially in the patient with a closed chest. Respirators of this type are employed primarily in anesthesia where apnea is frequently induced intentionally, although they could be modified for nonanesthesia uses. Examples of this type are the Bennett assistor-respirator (Fig. 4), the Emerson, the Stevenson, the Jefferson and the Morch.

Respirators applying pressure on the thoracic and abdominal walls. The outstanding example of this group is the iron lung. This formidable and bulky contrivance has practically outlived its usefulness and has been supplanted by other less unwieldly and more efficient units such as the *cuirass respirators* Emerson has modified the cuirass by a simple metal frame covered with a plastic sheet, thus converting the frame into a canopy which covers the chest and the abdomen (Fig. 5) These cuirass respirators apply a relative negative pressure to the chest and abdominal wall expanding the lungs forcefully (inspiratory phase) and then exerting positive pressure on the thoracic wall and abdomen forcing air out of the lungs An electric motor usually operates the mechanism powered either by house current or a battery These units have been employed mostly in patients with poliomyelitis, although they may be utilized in most any type of respiratory failure One of the big problems with the use of these units, especially in the unconscious patient, is maintaining a patent airway The cuirass respirators have recently been utilized for bronchoscopy performed under general anesthesia The patient is put to sleep and paralyzed with curare-like drugs Artificial respiration is then conducted with the cuirass respirator, and a patent airway is assured by the bronchoscope in the trachea This method of performing bronchoscopy has gained some enthusiasm

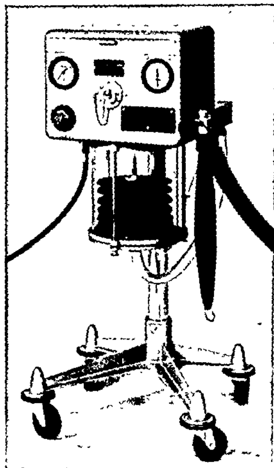


Fig 4 —Bennett anesthesia assistor respirator providing control of breathing frequency and the ratio of inspiratory duration to expiratory duration This unit provides negative as well as positive pressure

Special Problems Associated with Respiratory Failure

The Tracheostomy

When apnea suddenly supervenes, there frequently develops an agitated desire on the part of the attending physician to perform a tracheostomy. Although the thinking is sound and stems from the urge to provide an adequate airway, the logic is wrong. In the hands of the specialist who is well versed in this procedure, a certain amount of time lapses before a tracheostomy tube can be inserted through the artificial stoma In the hands of the novice, this time interval may be so prolonged as to cause permanent damage to brain cells or cause the death of the patient. It would be far simpler to institute mouth-to-mouth breathing, or insert an endotracheal tube, or apply a face mask and a breathing bag and immediately institute artificial respiration Meanwhile, better means of providing artificial respiration must be obtained and substituted for the initial method Only then can a tracheostomy be performed after a patent airway has been established and a steady method of artificial respiration instituted. True, instances of lives being saved by tracheostomy may be recounted, but the greater number of losses are unknown.

Various devices have been made to decrease the time needed in inserting a tube into the trachea. One such instrument is the tracheotome which consists of a tracheostomy tube with a sharp pointed insert. The desired tech-

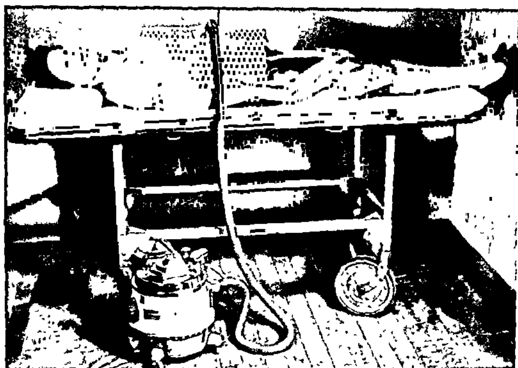


FIG. 5 —Emerson (plastic sheet) canopy chest respirator

nic involves the introduction of a big-gauged needle into the trachea This serves to guide the sharp-edged trocar of the tracheostomy tube, which follows into the tracheal lumen after the guide needle is withdrawn Familiarity with the technic is essential as a few serious complications have been reported. Another device is a small curved metal tube designed to penetrate the cricothyroid membrane This device may be useful in emergency situations but eventually may cause tracheal constriction A modification of this method is the insertion of a less traumatic large bore needle (13 gauge) through the cricothyroid membrane Oxygen is then introduced through this needle into the trachea. The value of these last two methods has been established by Draper and Whitehead[9] and Jacoby and associates[14] who have shown that in complete apnea, oxygen introduced into the tracheobronchial tree will be picked up efficiently by the blood stream through the action of the heart-hemoglobin pump. This is known as diffusion respiration The effectiveness of this method is at most 30 minutes, inasmuch as carbon dioxide will build up and cause respiratory acidosis.

The tracheostomy tube serves its greatest usefulness in the long term management of the patient with complete respiratory failure Once instituted, however, it brings up serious problems of nursing care such as keeping the tube from becoming plugged with secretions and mitigating the drying effects of air or oxygen on the tracheobronchial tree

The Patient with the "Crushed Chest" Injury

The greatest problem faced in this condition is the marked instability of the thoracic cage. Inefficient respiratory function is the outcome, which may be compounded by a hemothorax or a pneumothorax The hemothorax and the pneumothorax may easily be remedied. On the other hand, the chest instability severely interferes with breathing. In our hands, a tracheostomy is immediately performed. A special inner tracheostomy tube, such as the Mörch tube (FIG. 6), is employed. This is characterized by a side arm to which a respirator may be attached with a screw cap on top, the latter may be unscrewed for purposes of cleansing the tube and the tracheobronchial tree To bring stability to the thoracic wall, the tracheostomy is attached to a respirator such as the Mörch piston-pump type respirator, and the patient's breathing is paralyzed by increasing the rate and volume of the respirator. This hyper-

ventilation results in respiratory alkalosis with diminution of the effective carbon dioxide stimulus to breathing The increased volume also eliminates the Hering-Breuer reflex which controls ventilation to some extent. If this method of paralyzing respiration is ineffective and the patient manifests signs of resisting the respirator, then curare-like drugs, e g, succinylcholine, are employed to paralyze the peripheral respiratory muscles. The next question is whether respiratory alkalosis is harmful to the patient We have not found it so and have considered the optimum blood pH for this condition to be around 7.6. This is easily maintained by adjusting the respiratory rate and volume of air delivered by the respirator. No attempt is made to secure a tight fit of the tracheostomy tube in the trachea, as leaks around the tube may easily be compensated for by the volume of air delivered to the patient. Cleanliness of the tube and the tracheobronchial tree must be assiduously maintained by good nursing care such as frequent suctioning of secretions, irrigation with normal saline solutions in small amounts and humidification of the respired air with water or Alevaire or Tergemist Patients with "crushed chests" have been maintained in this condition for one to two months or until the fractured ribs have healed without any untoward complications. In fact, these patients eventually learn to talk and eat with the respirator actively functioning.

Pulmonary Edema

In this condition, fluid from the blood stream in varying amounts is suddenly released into the alveolar area. Under normal conditions, the lungs are capable of absorbing large quantities of fluid, so the fluid released in pulmonary edema cannot be too serious a problem. However, the fluid in pulmonary edema becomes frothy, which then interferes with gas interchange in the alveolar-capillary area This interference with gas exchange frequently causes cyanosis and hypoxia and contributes to the morbidity and mortality of the condition. The well established therapeutic measures include morphine, aminophylline, and hypertonic glucose, intravenous digitalization, tourniquets and venesection. Luisada[16] has also demonstrated the efficacy of antifoam agents such as ethyl alcohol Studies by our group[3] have shown that the silicone antifoam compounds are much more effective in breaking down the foam of pulmonary edema than ethyl alcohol. We have employed the silicone antifoam agents in the management of pulmonary edema especially in surgical cases with very great success. The silicone antifoam is nebulized and administered to the patient as an aerosol The use of an intermittent positive

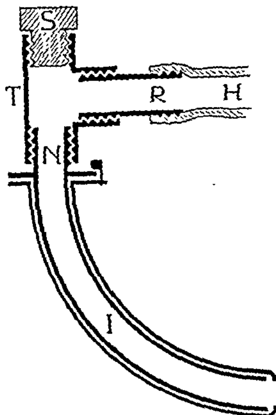


FIG 6—The Mörch-Saxton Tracheostomy Tube Connector (Anesthesiology 17: 366, 1956). I represents the inner cannula of a common Chevalier Jackson tracheostomy tube to which has been added a neck (N) with an outside thread. T represents a metal T-piece which screws onto the neck (N) permitting rotation The other vertical arm of the T-piece is closed by a screw-type stopper (S) of nylon or metal This stopper is unscrewed to permit aspiration The horizontal arm of the T-piece is connected to the rubber hose (H) from the respirator by means of a short-threaded piece of metal tubing (R) which is loose enough to permit rotation. This prevents torque in the respirator hose from twisting the tracheostomy tube

pressure breathing unit may help by diminishing venous return to the heart and by increasing the alveolar oxygen tension. Similar measures are indicated for other conditions in which failure of alveolar-capillary gas exchange is predominant.

Cardiac Arrest

Cardiac arrest is the term used for the condition in which there is dramatic and sudden cessation of effective mechanical cardiac systole Cardiac arrest may occur with either *cardiac* (ventricular) *asystole*, in which electrical systole is absent, or *ventricular fibrillation*, in which electrical systole is rapid and irregular, but in which mechanical systole consists only of fibrillary twitching without effective propulsion of blood In either case, the condition is extremely serious, and without effective treatment death will ensue within minutes

The causes of cardiac arrest fall into two categories the predisposing factors which may make the heart more susceptible to this catastrophe and the immediate provocative causes The following are considered the principal predisposing factors.

1 Cardiovascular disease.
2 Pulmonary disease.
3 Debilitating disease
4 Abnormal endocrine states

With the above conditions as a background, any combination of the following factors must be present in the myocardium to provoke the arrest:

1 Hypoxia
2 Hypercarbia
3 Reflexes
4. Anesthetic overdose which must be considered as a special factor in cases occurring in the operating room.

Predisposing Factors

Cardiovascular disease. The normal heart is capable of extracting oxygen maximally from blood. In abnormal situations as in severe hypotension, the coronary arteries can dilate to compensate for the diminished blood supply and divert more blood to the myocardium. The sclerotic coronary artery is incapable of responding in this manner. Thus, one can readily appreciate that this inability of the arteriosclerotic heart to compensate for the diminished blood supply during hypotensive episodes can easily result in severe myocardial ischemia and hypoxia. Coronary thrombosis and myocardial infarction may also occur in such a diseased heart after a severe hypotensive episode It has also been shown that in the diseased heart there seems to be an increase in the catechol amines—epinephrine and norepinephrine The catechol amines tend to favor the production of cardiac arrhythmias. DiPalma[8] demonstrated that an imbalance between acetylcholine and the catechol amines in rabbit myocardial strips appeared to provoke ventricular fibrillation Such fibrillation may easily be reverted by restoring the balance between acetylcholine and the catechol amines In the diseased heart, there is definitely an imbalance due to the predominance of catechol amines[20] This may explain, at least in part, the clinical observation that the diseased myocardium develops ventricular fibrillation much more frequently than the normal myocardium, when exposed to severe stresses such as hypoxia, hypercarbia, hypotension and possibly noxious vagal reflexes

Vascular disease, particularly hypertension, diminishes the affected individual's ability to compensate for changes in his homeostasis Having adjusted themselves to a higher pressure, vital organs such as the heart, brain, kidneys and liver become very susceptible to hypotensive episodes Hypotension in a hypertensive individual very quickly results in a diminished cardiac output with subsequent coronary insufficiency and myocardial hypoxia. Thrombosis with embolic phenomena may also occur as a result of hypotension particularly if there is appreciable arteriosclerosis

Pulmonary disease. There are two main circumstances in which pulmonary diseases may affect cardiac function The first of these is related to gas exchange, i e , the absorption of oxygen and the elimination of carbon dioxide Interference with this function can only lead to hypoxia and hypercarbia. During hypoxia, the myocardium, which always extracts oxygen maximally, suffers readily. Hypercarbia, on the other hand, may diminish the contractile

power of the myocardium and possibly lend greater susceptibility to noxious vagal reflexes. The second function of the lungs concerns that volume of blood which has been termed either central blood volume or thoracic blood volume. The amount of blood available in this volume influences greatly the stroke output of the heart and thus to a considerable extent the cardiac output Pulmonary conditions which reduce the central blood volume must of necessity diminish this cardiac reserve

Endocrine disturbances Several endocrine disturbances may in part predispose to cardiac arrest Patients with thyrotoxicosis, especially when atrial fibrillation is present, are susceptible to cardiac arrest Diabetes mellitus with its accompanying disturbances of metabolism may affect myocardial function The metabolic acidosis of uncontrolled diabetes also predisposes to cardiac arrhythmias In preparing diabetic patients for surgery, failure to change from the long-acting or oral insulin preparations may inadvertently bring about an episode of hypoglycemic shock of which the operator and the anesthetist are unaware. Adrenocortical insufficiency is potentially able to affect the heart rhythm The additional stress of surgery and anesthesia will frequently throw these patients into shock and often sudden death

Hemorrhage, hemorrhagic shock and the debilitated patient These three categories are discussed together primarily because all three of the conditions exhibit a diminished circulating blood volume When the hemorrhage is slow and gradual, compensation is usually achieved by constriction of the vascular bed and the diffusion of fluid from the tissues into the blood stream, if hemorrhage is rapid, compensation may be inadequate, shock will supervene, and myocardial ischemia will result In the debilitated patient, there is a small circulating blood volume in a constricted vascular bed[6] In such patients, the vascular function is very critical and any stress placed on it, such as deep anesthesia, surgery or hemorrhage, may cause myocardial failure and arrest

Certain types of shock do not fall into the above pathophysiologic pattern Examples of these are anaphylactic, nervous or emotional shock Although the blood volume is not reduced in these conditions, dilatation of the vascular bed may have slowed the circulation so that venous return to the heart and cardiac output are diminished, and coronary flow is decreased with subsequent hypoxia of the myocardium It is during conditions in which hypoxia and hypercarbia coexist in the myocardium that the heart is most vulnerable to noxious reflexes and consequent arrest

Provocative Causes of Cardiac Arrest

Hypoxia Hypoxia occurs as a result of insufficiency of either alveolar ventilation, alveolar-capillary diffusion or ventilation blood flow distribution Hypoxia may be acute and sudden, or slow and insidious It may be chronic When it occurs suddenly, as in acute obstruction of the tracheobronchial tree, the condition may be quickly recognized and ameliorated In the operating room, sudden acute obstruction may be due to secretions, foreign body impinging against the larynx, aspiration of blood or vomitus, mechanical obstruction of the artificial airway or surgical manipulation especially along the course of the tracheobronchial tree Cyanosis may become manifest in severe hypoxia but is not a reliable sign inasmuch as minor degrees may be unrecognizable Partial obstruction which is slow and insidious may be ignored or go unrecognized for long periods of time

Chronic hypoxia may be present in chronic diseases of the lungs such as bronchial asthma, emphysema or other conditions in which the respiratory efficiency has been impaired In this situation, the myocardium has probably achieved a critical degree of adjustment so that further hypoxia may actually push the heart into arrest Experimental studies on dogs show ventricular fibrillation to occur with greater frequency in the chronically hypoxic animal[22]

Hypercarbia The primary stimulant of the respiratory center is carbon dioxide which is also one of the chief waste products of metabolism In normal individuals, the CO_2 tension in both the alveolar air ($P_{A_{CO_2}}$) and the arterial blood (Pa_{CO_2}) are maintained within a relatively narrow range (37 to 43 mm Hg) Excess

CO_2 stimulates increased ventilation to bring the CO_2 back within the normal range. Lower than normal P_{CO_2}, on the other hand, results in hypopnea or even apnea to increase carbon dioxide concentration Hypercarbia is more deleterious to the heart than is hypocapnia Experimental studies in dogs have shown that hypercarbia increases the incidence of cardiac asystole on vagal stimulation [23] Hypercarbia also results in decreased contractility of the myocardium and may result in progressive hypotension [19] Serum potassium increases progressively in dogs made hypercarbic, in part due to release of epinephrine [24] Miller and coworkers[19] exposed dogs to high carbon dioxide atmospheres for several hours and then suddenly ventilated them with room air Increased cardiac irritability including ventricular fibrillation and cardiac standstill quickly occurred in these animals Such a phenomenon has been observed in the patient whose airway is chronically and severely obstructed Hypercarbia seems to sensitize the myocardium to vagal reflexes more than hypoxia Whether or not hypercarbia is more dangerous than hypoxia, a combination of both greatly increases the susceptibility of the myocardium to arrest

Reflexes. The heart and its contiguous structures are well endowed with reflex receptors. The efferent arms of these reflex mechanisms to the heart are usually the sympathetic nerves and the vagi. The more harmful reflexes are usually mediated through the vagus Under normal conditions, most of these reflexes are not harmful to the myocardium In the presence of hypoxia and hypercarbia, they may become quite deadly Such reflexes may arise from such stimuli as manipulations around the pulmonary hilum, traction of mesentery, inadvertent pressure on the eyeballs, endotracheal intubation, tracheobronchial suction or rectal dilatation The anesthetic agent employed may contribute to the sensitivity of the myocardium to vagal reflexes

Of particular interest is the type of cardiac arrest which results from a myocardial infarction or a massive pulmonary embolism. This may be related to the reflexes originally described by Bezold and Jarisch[1] in which stimulation of chemoreceptors in the coronary or pulmonary vessels resulted in (1) bradycardia to arrest, (2) hypotension and (3) hypopnea to apnea. Although these reflexes have never been specifically identified in humans, clinical evidence suggests that responses similar to the Bezold-Jarisch reflexes occur in man. It has been demonstrated in animals that serotonin is capable of stimulating these reflexes.[7] It has been postulated that in myocardial infarction and in pulmonary embolism, sufficient amounts of serotonin may be released from the blood to stimulate reflexes similar to the Bezold-Jarisch reflexes [19]

General anesthetic agents Most general anesthetic agents with the exception of nitrous oxide are capable of stimulating the vagus nerves both centrally and peripherally and of depressing the myocardium directly. Ether has always been considered a sympathomimetic agent; however, there is evidence to show that in light ether anesthesia the vagal centers are stimulated by it, and a few cases of cardiac arrest have been attributed to this effect Most of the general anesthetic agents will cause a progressive dilatation of the vascular bed especially in deep anesthesia Most of them (particularly cyclopropane, chloroform, ethyl chloride and possibly halothane) may increase the irritability of the myocardium especially in the presence of epinephrine [17] Deep anesthesia will depress respiration with concomitant hypoxia and hypercarbia unless breathing is assisted or augmented A metabolic acidosis has been demonstrated with the use of ether and chloroform and possibly with the other agents [10]

Management of Cardiac Arrest

Prevention of cardiac arrest is always desirable Prevention starts with the preoperative preparation of the patient All of the predisposing conditions such as hypovolemia, anemia, malnutrition, cardiac and pulmonary disease should be treated and improved as much as possible. Unless the prevailing situation imperils the patient's life in an urgent manner, all possible preparation should be undertaken to bring the patient to the operating room in the best condition possible.

Signs of impending cardiovascular collapse. In the patient under anesthesia, changes in the

heart rate such as a progressive tachycardia or a severe bradycardia may be the first sign of impending shock Changes in skin color such as paleness or a pale cyanosis usually indicates a failing myocardium Sweating and tachypnea may develop with embolic phenomenon to the brain, heart or lungs The pulse and the blood pressure are good indices of the status of the cardiovascular system Changes in the strength of the pulse beat and its compressibility are important signs in addition to changes in the rate and irregularities in rhythm The pulse usually becomes fast and highly compressible in early shock Monitoring devices such as the electrocardiograph may be helpful in early recognition of these rate changes or irregularities in rhythm On the other hand, a good normal electrocardiogram is not always indicative of functional integrity. We have observed normal electrocardiographic patterns in patients with severe hypotension, although if prolonged, the patterns will eventually be those of myocardial ischemia

Diagnosis of cardiac arrest As soon as the absence of a palpable pulse or blood pressure is announced, two provocative tests are immediately utilized

1 Vasopressor-atropine test 1 0 to 3 0 mg of Phenylephrine (Neosynephrine) with atropine 1 0 mg is immediately injected into a fast intravenous infusion If circulatory insufficiency alone is present with a weakly beating heart, this mixture will immediately stimulate the heart and improve circulation Pulse beats and blood pressure become immediately palpable Phenylephrine exerts a reflex bradycardia on the heart and constricts the vascular bed However, it is very quick acting and its effect is evanescent Isopropylnorepinephrine (Isuprel) is a very potent stimulant of the myocardium It also has the ability to dilate peripheral blood vessels and possibly cause hypotension The use of phenylephrine with the isopropylnorepinephrine offsets its hypotensive effects The atropine in the mixture is used to counteract any possible vagal stimulation

2 An incision is made into a relatively larger blood vessel if available for signs of active bleeding, otherwise the incision is made at the site where entry into the left chest is contemplated (fourth or fifth left intercostal space—anterior-axillary line). Signs of active arterial bleeding are sought If present, nothing has been lost, and the chest is not entered If absent, entry into the chest is very quickly made

Active Management of the Cardiac Arrest

Artificial respiration with an endotracheal tube, anesthesia face mask or even mouth-to-mouth respiration is recommended until better methods become available This procedure should be started at the time of the provisional diagnosis. In the anesthetized patient, all anesthetic agents should have been stopped and only oxygen administered

Entry into left chest The site of incision is made at the fourth or fifth interspace just left of the left sternal border at the midclavicular line extending into the axillary area Preoccupation with sterile technic is unwise since speed is essential The costochondral cartilages above and below the point of entry are cut so as to enable the insertion of a rib-spreader. A rib-spreader enlarges the opening through which the operator performs manual cardiac systole

Manual cardiac systole This is immediately started outside the pericardium, if possible, but if not effective, the pericardium may be opened. Massage should be started from the apex of the heart and blood milked to the base. If the heart is small, it may be grasped in the palm of the hand If large, it may be compressed against the sternum. The thenar eminence and not the thumb should be employed in compressing the heart. We have observed instances where the thumb inadvertently ruptured one of the atria The rate should be as fast as the operator can achieve, at the same time maintaining effective stroke output This procedure is tiring if performed effectively, so one or two other persons must be ready to alternate with the operator. For this procedure to be effective, a peripheral pulse (carotid or superficial temporal) must be palpable with every compression of the heart.

Drug therapy. Calcium chloride 10 per cent. If the heart is in asystole, it may be encouraged to beat by injecting 5 to 10 ml of calcium chloride 10 per cent into either ventricle. Calcium chloride may improve the tone of the myo-

cardium and to some extent will counteract the effects of previously injected potassium chloride

Isopropylnorepinephrine (Isuprel) This drug has been found to be a very potent stimulant of the myocardium It may be injected intravenously or intraventricularly in doses of 0.02 mg (1:5000) If effective, it may cause a marked tachycardia and a peripheral vascular dilatation. Phenylephrine (Neosynephrine) should be administered at the same time in order to prevent hypotension

Potassium chloride 10 per cent. This drug is employed in the presence of ventricular fibrillation It is also injected into the ventricular chamber in amounts varying from 2 to 5 cc. Calcium chloride may be needed to counteract the asystole which may be induced

Epinephrine (1:1000) Epinephrine, like isopropylnorepinephrine, is a potent stimulant of the myocardium. It does tend to induce ventricular fibrillation. Beck has advocated the use of procaine 1 per cent with epinephrine to prevent this complication [3]

Procaine 1 per cent This drug is a true myocardial depressant. It prevents ventricular fibrillation by depressing the myocardium directly. It is very rarely employed for defibrillation purposes.

Molar sodium lactate Bellet and associates[4] have recommended molar lactate for restoring heart beat in cardiac arrest and in Stokes-Adams syndrome Given intravenously, it may work successfully

Defibrillation. Ventricular fibrillation is characterized by a "worm-like" movement of the myocardium and may be indicative of a nonfunctioning conduction system with other independent foci taking over the initiation of heart beat. It is an ineffective beat and from the standpoint of propulsion of blood, the heart is at a standstill Defibrillation may be accomplished with potassium chloride (10 per cent) and the heart beat restarted with calcium chloride Defibrillation may also be performed with an electric defibrillator (Figs. 7 and 8) which uses a tetanizing shock to induce a single vigorous contraction followed by cardiac arrest. A current of 1.0 to 2.0 amperes is necessary for effective defibrillation. This current flows rapidly through the heart between two flat or concave metal electrodes 1 to 1½ inches in diameter. To develop 1 to 2 amperes of current in hearts with variable electrical resistance, a variable transformer is necessary which can convert 115 volt current to voltages ranging from 60 to 200 volts. The average resistance of the myocardium is 50 to 60 ohms, but larger hearts offer greater resistance to current flow, thus requiring higher voltage for effective shocking current. The electrical shocks are usually at least 0.1 second in duration. A longer period of shock may result in an epicardial burn. We prefer to administer a series of three shocks in rapid succession to a normal or small heart but in large hearts may increase this to five or six shocks with shift of the positions of the electrodes to prevent local burns.

Occasionally, ventricular fibrillation may persist Defibrillation may be successful in the early stages of cardiac resuscitation, but the heart may repeatedly revert to fibrillation The prognosis in these cases is poor. Manual systole has been carried out for two to three hours in some such cases with unfavorable results. The myocardium becomes bruised in prolonged manual systole We have observed persistent ventricular fibrillation in which the conduction system may have been cut inadvertently or ligated, and in instances of prolonged hypoxia The problem of therapy in these cases is the length of time manual massage should be continued when ventricular fibrillation persists. Only rarely will there be recovery when ventricular fibrillation persists for as long as two hours except for the heart in hypothermia Nevertheless, as long as the heart reverts to occasional episodes of regular rhythm after defibrillation, resuscitation is continued.

The cardiac pacemaker (Fig. 8) Although we have occasionally restarted a heart with the pacemaker, we have failed more times than we have succeeded. In one instance, we were able to maintain a regular heart beat in a child with cardiac arrest without entering the chest. After about a half hour with this method, the heart became refractory to the electrical impulse from the pacemaker. We have not had the degree of success with the pacemaker that has been reported by other groups It is possible that some

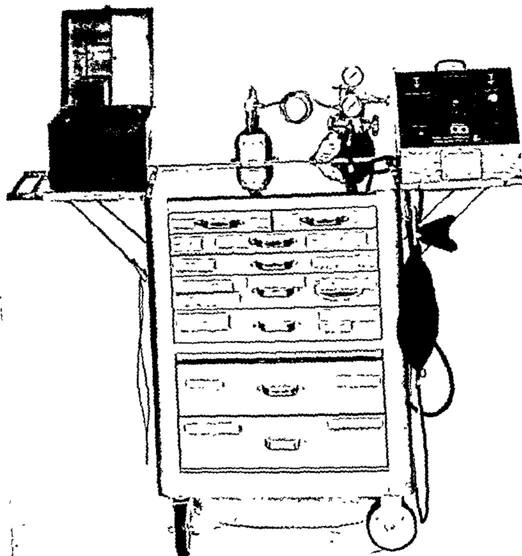


Fig 7—An emergency cart with cardiac defibrillator and an electrocardiographic apparatus

of the claimed successes were actually cases of profound cardiac insufficiency (with no demonstrable pulse or blood pressure) instead of actual cardiac arrest

We have found the pacemaker particularly useful in the *faltering heart* After cardiac surgery in some instances or after successful resuscitation of an arrested heart, bradycardia or cardiac irregularities may ensue In these hearts, the pacemaker often can prevent complete cardiac arrest, and these hearts may be kept beating regularly with the pacemaker until they stabilize and contract regularly without assistance Electrodes may be left in the chest wall at the second or third interspace at both borders of the sternum, or one wire electrode may be left in the myocardium and the other sewn into the chest wall Portable transistorized pacemakers powered by dry cell batteries are available today for this purpose These transistorized pacemakers are proving practical and effective

Closure of the chest If it appears that the heart has been successfully resuscitated and is now beating vigorously, effectively and regularly, with a measurable blood pressure, and if the patient is initiating his own breathing, closure of the chest should be considered First,

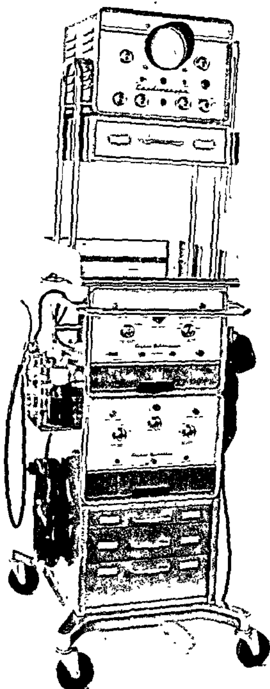


FIG 8—An electrical defibrillator and cardiac pacemaker on an emergency cart At the top is a cardioscope to monitor the electrocardiogram

however, the heart must be observed for at least 30 minutes to see that it does not stop once more or develop irregularities in rate or rhythm. The pericardium may be closed with a small opening left to allow drainage of any accumulated fluid; but the opening must not be large enough to allow herniation of the heart through it. The chest may then be closed in the usual manner. It may be wise in some instances to embed wire electrodes from the pacemaker in the chest wall or in the myocardium itself in case further arrhythmias or arrest develop

The after-care. Respiratory function An open airway must be zealously maintained. This may be accomplished by frequent tracheobronchial toilets or suction of the airway, particularly if an endotracheal tube or a tracheostomy tube is left in place The majority of cardiac arrest patients have undergone a hypoxic episode and probably have a depressed respiratory center. If respirations are inadequate, the endotracheal tube may be left in place for the next 24 to 48 hours—no longer Ulcerations in the trachea may develop from the endotracheal tube remaining much longer Should the patient still not be able to maintain an open airway, a tracheostomy should be performed This will allow secretions to be more easily suctioned and the tracheobronchial tree regularly irrigated with normal saline solution. If respiratory exchange is inadequate, an intermittent positive pressure breathing unit must be employed to assist and, if necessary, take over respiration Oxygen may be given if existing or impending hypoxia is diagnosed. The use of aerosols, like Alevaire or Tergemist or even plain distilled water, has helped to liquefy thickened secretions and to prevent drying of the tracheobronchial tree When bronchiolar constriction is suspected or observed, isopropylnorepinephrine is nebulized for inhalation by the patient Atelectasis may be prevented by the regular use of the positive pressure breathing unit, if not already being utilized.

Cardiovascular function The heart rate and rhythm should be monitored electrocardiographically, and the blood pressure must be maintained Blood loss, if any, should be replaced and blood volume determinations obtained, if necessary, to prevent overtransfusion and possible heart failure and pulmonary edema. There should be no hesitancy in utilizing vasopressors to maintain blood pressure The milder vasopressors, like phenylephrine (Neosynephrine) or metaraminol (Aramine), should be employed, preferably as an intravenous drip. We have used 10 to 50 mg. of phenyl-

ephrine in 1,000 ml of dextrose 5 per cent in water for this purpose. If the above vasopressors are ineffective, norepinephrine (Levophed) may be employed. The addition of hydrocortisone will frequently improve the pressor response of the patient to vasopressors, possibly because of mobilization of potassium at the pressor receptor sites rendering them more responsive to the vasopressor.

Electrolyte and fluid balance should be maintained An indwelling catheter is left in the bladder and fluid intake and output carefully measured

Care of the brain It is believed that after an hypoxic episode, the brain frequently develops edema which may prevent or prolong return to consciousness Since the brain is vital in the eventual recovery of the patient, all means possible should be employed to facilitate its ability to recuperate

Monitoring the brain with the electroencephalogram has proved useful in assessing response of the brain to therapy The amplitude and frequency of certain brain waves signifying light sleep or consciousness may completely disappear in severe hypotension or in excessive brain edema An adequate blood pressure is quickly manifested by an improvement of depressed EEG patterns The EEG can also serve as an index of improvement or recovery of the brain

Urea has the capacity for drawing water out of the tissues in addition to being a powerful diuretic Urea has been utilized successfully to diminish brain edema in doses of 0 5 Gm per kilogram of body weight repeated every 6 to 8 hours The only contraindication to its use is kidney shutdown By drawing fluids into the bloodstream, urea also tends to raise the blood pressure

Some degree of success has been reported with the use of hypothermia, which appears to have increased the incidence of recovery of patients resuscitated from cardiac arrest Hypothermia diminishes over-all metabolism, and this seems to be beneficial to patients who have undergone great stress For patients resuscitated from cardiac arrest, we have employed mild hypothermia, reducing body temperature with a cooling blanket down to 94 or 95 F The patient occasionally shivers during the process of cooling, and such may be harmful to the patient in the sense that it increases metabolic rate in his attempt to counteract reduction of body temperature. Cooling is also good for the hyperthermia that occasionally occurs or develops after a hypoxic episode.

When convulsions develop after the hypoxic episode, Dilantin sodium has been employed to control them. The dose varies from 50 mg. to 200 mg and is repeated as needed to control the seizures.

Care of other organs. (1) The eyes should be covered with vaseline gauze to prevent drying. (2) A Foley indwelling catheter is left in the bladder. (3) A Levine tube is inserted into the stomach and mild suction instituted. This prevents accumulation of gas and secretions in the stomach but may also disturb the patient's electrolyte balance (4) The patient should be moved from side to side and left in this position for intervals of time to prevent decubitus ulcers

Resuscitation is usually associated with a sense of urgency. Immediate decisions are demanded by the situation The outcome is difficult if not impossible to predict and depends on many circumstances associated with the occurrence of the event—some of which might not even have been appreciated at the time. Thus, the success or failure of the resuscitative effort is not necessarily a measure of the efficacy of the technic employed Unwarranted optimism may be assumed by those who may have had a few successes, whereas a cynical and even dismal attitude may be displayed by those who have experienced more failures than sucesses. Although enthusiasm must be restrained, a negativistic approach is certainly not the answer The mere fact that successes, no matter how small the percentage in relation to failures, fully justify a trial of resuscitative effort in any situation in which the only alternative is immediate death

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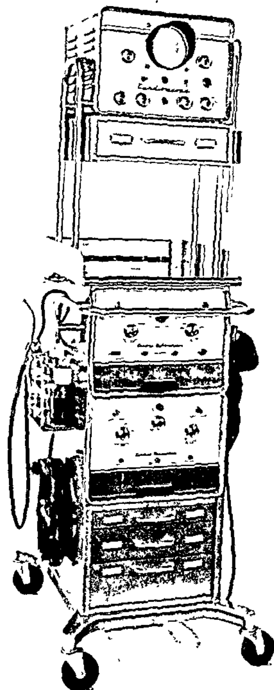


FIG 8—An electrical defibrillator and cardiac pacemaker on an emergency cart At the top is a cardioscope to monitor the electrocardiogram

however, the heart must be observed for at least 30 minutes to see that it does not stop once more or develop irregularities in rate or rhythm. The pericardium may be closed with a small opening left to allow drainage of any accumulated fluid, but the opening must not be large enough to allow herniation of the heart through it. The chest may then be closed in the usual manner. It may be wise in some instances to embed wire electrodes from the pacemaker in the chest wall or in the myocardium itself in case further arrhythmias or arrest develop

The after-care. Respiratory *function.* An open airway must be zealously maintained. This may be accomplished by frequent tracheobronchial toilets or suction of the airway, particularly if an endotracheal tube or a tracheostomy tube is left in place The majority of cardiac arrest patients have undergone a hypoxic episode and probably have a depressed respiratory center. If respirations are inadequate, the endotracheal tube may be left in place for the next 24 to 48 hours—no longer. Ulcerations in the trachea may develop from the endotracheal tube remaining much longer. Should the patient still not be able to maintain an open airway, a tracheostomy should be performed This will allow secretions to be more easily suctioned and the tracheobronchial tree regularly irrigated with normal saline solution If respiratory exchange is inadequate, an intermittent positive pressure breathing unit must be employed to assist and, if necessary, take over respiration Oxygen may be given if existing or impending hypoxia is diagnosed The use of aerosols, like Alevaire or Tergemist or even plain distilled water, has helped to liquefy thickened secretions and to prevent drying of the tracheobronchial tree When bronchiolar constriction is suspected or observed, isopropylnorepinephrine is nebulized for inhalation by the patient. Atelectasis may be prevented by the regular use of the positive pressure breathing unit, if not already being utilized.

Cardiovascular function The heart rate and rhythm should be monitored electrocardiographically, and the blood pressure must be maintained Blood loss, if any, should be replaced and blood volume determinations obtained, if necessary, to prevent overtransfusion and possible heart failure and pulmonary edema. There should be no hesitancy in utilizing vasopressors to maintain blood pressure. The milder vasopressors, like phenylephrine (Neosynephrine) or metaraminol (Aramine), should be employed, preferably as an intravenous drip. We have used 10 to 50 mg of phenyl-

ephrine in 1,000 ml. of dextrose 5 per cent in water for this purpose. If the above vasopressors are ineffective, norepinephrine (Levophed) may be employed. The addition of hydrocortisone will frequently improve the pressor response of the patient to vasopressors, possibly because of mobilization of potassium at the pressor receptor sites rendering them more responsive to the vasopressor

Electrolyte and fluid balance should be maintained An indwelling catheter is left in the bladder and fluid intake and output carefully measured.

Care of the brain It is believed that after an hypoxic episode, the brain frequently develops edema which may prevent or prolong return to consciousness Since the brain is vital in the eventual recovery of the patient, all means possible should be employed to facilitate its ability to recuperate

Monitoring the brain with the electroencephalogram has proved useful in assessing response of the brain to therapy The amplitude and frequency of certain brain waves signifying light sleep or consciousness may completely disappear in severe hypotension or in excessive brain edema. An adequate blood pressure is quickly manifested by an improvement of depressed EEG patterns The EEG can also serve as an index of improvement or recovery of the brain

Urea has the capacity for drawing water out of the tissues in addition to being a powerful diuretic Urea has been utilized successfully to diminish brain edema in doses of 0 5 Gm per kilogram of body weight repeated every 6 to 8 hours The only contraindication to its use is kidney shutdown By drawing fluids into the bloodstream, urea also tends to raise the blood pressure

Some degree of success has been reported with the use of hypothermia, which appears to have increased the incidence of recovery of patients resuscitated from cardiac arrest Hypothermia diminishes over-all metabolism, and this seems to be beneficial to patients who have undergone great stress For patients resuscitated from cardiac arrest, we have employed mild hypothermia, reducing body temperature with a cooling blanket down to 94 or 95 F. The patient occasionally shivers during the process of cooling, and such may be harmful to the patient in the sense that it increases metabolic rate in his attempt to counteract reduction of body temperature Cooling is also good for the hyperthermia that occasionally occurs or develops after a hypoxic episode.

When convulsions develop after the hypoxic episode, Dilantin sodium has been employed to control them The dose varies from 50 mg to 200 mg. and is repeated as needed to control the seizures

Care of other organs. (1) The eyes should be covered with vaseline gauze to prevent drying. (2) A Foley indwelling catheter is left in the bladder. (3) A Levine tube is inserted into the stomach and mild suction instituted. This prevents accumulation of gas and secretions in the stomach but may also disturb the patient's electrolyte balance (4) The patient should be moved from side to side and left in this position for intervals of time to prevent decubitus ulcers.

Resuscitation is usually associated with a sense of urgency. Immediate decisions are demanded by the situation The outcome is difficult if not impossible to predict and depends on many circumstances associated with the occurrence of the event—some of which might not even have been appreciated at the time Thus, the success or failure of the resuscitative effort is not necessarily a measure of the efficacy of the technic employed Unwarranted optimism may be assumed by those who may have had a few successes, whereas a cynical and even dismal attitude may be displayed by those who have experienced more failures than sucesses Although enthusiasm must be restrained, a negativistic approach is certainly not the answer The mere fact that successes, no matter how small the percentage in relation to failures, fully justify a trial of resuscitative effort in any situation in which the only alternative is immediate death

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Section V

PULMONARY PHYSIOLOGY—GENERAL CONSIDERATIONS

The Beginnings of Pulmonary Physiology

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LIFE is short and the art long, occasion instant, experiment perilous, decision difficult Students of pulmonary physiology cannot too often read the lines of this familiar aphorism, unbettered in our modern day, without realizing the virtues of an abiding interest, painstaking research and thoughtful evaluation. The ideals are sometimes challenged by the pressures for an immediate explanation or a timely solution As a counterpart, history reveals that no one of the countless investigators knows for certain whether the mantle of recognition will fall on his shoulders and gain for him even a mild distinction or satisfaction Certainly, the God-given privilege of becoming a renowned benefactor is reserved for few men, much less are the prospects that his contributions will be accepted and furthered

Investigations of pulmonary disease in ancient times were halting and irregular even in the golden age of Greece, with its intellectual giants and deeply interwoven culture On occasion, perhaps, the discoveries were obscured by excursions into philosophy, poetry and the supernatural, thus impairing their value to fundamental and applied science Still, in this slowly developing evolution, there was generated here and there a figure or an idea, destined to become profoundly important for succeeding generations These are revealed as the stepping stones to an era—our present day—with intriguing projects, masterful teamwork, technical apparatus, computor retrieval systems, basic technics

Greek medicine during the time of Hippocrates (460-370 B.C.) reached the heights It became an art, a science *and a profession, with* Hippocrates, as an inspiring writer, instigator and moving spirit. He stimulated and utilized the brain power of the day He sought to divorce philosophy from medicine and strongly criticized the healing shrines, demoniac possession and supernatural medicine. Although Hippocrates was deeply concerned with medicine, his concepts of physiology only vaguely suggested the nature and influences of disease and the basic disturbances

Excerpts from the writings of Hippocrates, as quoted from Major, give an inkling of his way of thought:

> "In hydrops of the lung you will find on listening with one ear against the chest it boils like vinegar," suggesting to historians that he recognized the presence of bronchiolar affections or pulmonary edema And in another passage he wrote "The vessels pass throughout the entire body, give it air, fluid and movement by these vessels we take in the greater part of our breath, for they are the vents of our body, drawing air to themselves and they spread it over the body in general through the minor vessels *and* cool it; then they breathe again "

Thus, Hippocrates in these statements was the first to suggest that the air which passed into the lungs served merely to cool the heart. Aristotle (384–322 B.C.) agreed with this concept, and four centuries later Galen (138-201 A D) echoed these beliefs and pointed out that the cooling of the heart was important, *for this* organ would be destroyed by the heat which it generated.

There was a lapse of four centuries before the advent of Galen, the prototype of the modern investigator and imperiously self-confident "successful practitioner " Galen was a Greek, born in Pergamum, Asia Minor, and his medi*cal studies were started* at the healing shrine in that city. He then proceeded to Smyrna,

where he remained for two years before moving to Alexandria, the center of the Greek world. Galen was dissatisfied with his medical course as "The art of medicine was taught by ignoramuses . . to crowds of fourteen year old boys who never go near the sick" On returning to Pergamum he entered medical practice and simultaneously became interested in physiology Galen believed that pneuma passed into the trachea, over the pulmonary vein and then entered the left ventricle of the heart. The blood also passed through the vena cava into the right side of the heart where the various impurities were discharged through the pulmonary artery into the lungs for exhalation through the trachea William Harvey, fifteen centuries later, wondered why Galen did not recognize the implications of his own observations and discover the circulation of the blood Galen's most important teachings in respiratory physiology dealt with the mechanics of breathing, e g , the phenomenon characterized by two acts—the contraction of the diaphragm through the influence of the phrenic nerve and movements of the chest wall as related to the intercostal muscles.

There followed a barren period of some fourteen centuries wherein the truths and errors of Galen continued to dominate thought. Then suddenly the sixteenth century bloomed in grandeur as the Renaissance, with its galaxy of medical investigators and feeders of medical thought Of the outstanding personages, no less than seven were Italians and nearly all of them were contemporaries It was fortunate that the heroes were the anatomists, including Leonardo da Vinci (1452–1519), whose dissections of the heart and blood vessels set the stage for the soundest possible approach to pulmonary physiology An encouraging feature was the attempt to display graphically the pathways of air and blood in the body Da Vinci believed that pure air was necessary both to animal life and the "burning flames—where flames cannot live no animal that breathes can sustain interest."

It was the belief of ancient physicians that the blood somehow flowed from the right to the left ventricle, but the mechanisms remained obscure Galen, for example, had suggested that the blood passed through invisible pores in the intraventricular septum. Denial of this concept by Ibn an-Nafis in the 13th century (1210–1288) was the outstanding contribution to this field between the time of Galen and the Renaissance, although until recent years this work was largely unrecognized Ibn an-Nafis was dean of the Mansoury Hospital in Cairo and in his commentary on Avicenna's "Anatomy" correctly deduced the general nature of the pulmonary circulation Three centuries later Michael Servetus (1509–1553) independently discovered the pulmonary circulation and suggested that the blood was transmitted from the pulmonary artery into the pulmonary vein by a "lengthened passage through the lungs in the course of which it is elaborated and becomes crimson " Six years later, Renaldo Columbo (1516–1550) arrived at a similar conclusion and gained a degree of priority in stating that the blood is carried by the pulmonary artery to the lungs, from whence it takes up the air for transport through the pulmonary vein to the left ventricle of the heart It is interesting that the heart and lungs were identified at this time as a functioning unit, as association to be repeated during the later developments of cardiopulmonary physiology.

Another celebrated Italian anatomist, Andrea Caesalpino (1524–1603), Professor of Medicine at Pisa, is credited by some[10, 11] as the discoverer of the circulation Fifty-seven years before the published reports of Harvey, Caesalpino suggested the possibility of a constant and physical transit of blood from the arteries to the veins by anastomoses, termed *vasa in capillamanta resulta* This perpetual forward movement of the blood from the vena cava to the right heart, thence to the lungs, from the lungs to the arteries to every part of the body, he later called *circulato* The actual formulation of the concept of circulation in a more detailed and over-all fashion was in the work, *De Motu Cordis*, published in 1628 by William Harvey (1578–1657) Harvey, an Englishman, was born in Folkestone, studied anatomy at Padua and received the degree of Doctor of Medicine from Cambridge Whether or not Harvey deserves full credit for discovery of the circulation, he undoubtedly formulated more completely and understandably the basic concepts of the func-

tions of the heart and circulation as a well-ordered and purposeful system It was Harvey who definitely established the relationship of the general circulation and the lungs and he did so with clarity and critical evaluation.

Revelations of pulmonary physiology up to the time of Borelli disclosed two important views Galen's belief that the lungs expand with the chest as air is naturally drawn into them, and Robert Boyle (1627–1691) who held that the lungs are filled with air because the chest dilates. Boyle also believed that the diaphragm and intercostal muscles play a significant role in the act of respiration He further conceived that a given mass of air at a given temperature varies in volume inversely with the pressure. Boyle became interested in respiratory problems and prevailed upon Robert Hooke to assist him in the construction of an air pump. The significance of his work concerns the phenomenon that birds and mice, placed in a chamber, die promptly when the air is removed with a pump "We may suppose that there is in air a little vital quintessence . which serves to the refreshment and restoration of our vital spirits "

The term physiology was rarely employed in ancient times, coming into general use during Borelli's day (1608–1679) It was Borelli[2] who enriched the science with his basic knowledge of physics, mathematics and physical methods, presented in a clear, logical and incisive manner. He recognized that inspiration occurs as a result of the enlarged thoracic cage, associated with the phenomenon of ambient atmospheric pressure. His observations resolved the question of how the muscles expand the thoracic chamber, and in further investigations he pointed out that the normal expiration was essentially passive in type, the result of cessation of muscular contraction This was "advanced thinking," for even in our day it is mentioned erroneously that air is discharged during expiration by the "squeezing" mechanism of the chest. He dismissed the earlier views that ventilation was the phenomenon of "cooling the heart;" and, not least, he clearly pointed out that particles of air drawn into the lungs become mixed with blood He rejected, however, the suggestion that chemical substances were drawn from the air as had been suggested by English physiologists

In 1667, Robert Hooke presented the observation that movements of the chest wall were unnecessary for the maintenance of life in the experimental dog with an open thorax, if the lungs were artificially ventilated: and even with a punctured lung the dog lives when air is intertracheally introduced by bellows His studies confirmed the observations of Vesalius in proving that the pertinent factor of respiration is not in the intrinsic movements but in certain alterations of the blood, a concept that has entered into our technics of artificial respiration

The experiments of Robert Hooke were carried further by Richard Lower (1631–1690) who proved that fresh air in the lung will change the color of blood from dark to bright red, suggesting basically that air is removed in the tissues

A far-reaching step in the elucidation of pulmonary physiology was the discovery of oxygen Joseph Priestly, in 1772, isolated the gas and identified its properties,[9] but unfortunately he failed to comprehend its true significance because of his adherence to the phlogiston theory He believed that when a candle burns out in a closed jar it is due to the saturation of phlogiston, rather than the presence of a chemical combination It remained for Antoine-Laurent Lavoisier (1743–1794), in 1780, to overthrow the phlogiston theories and to establish the elemental character of the gas. Lavoisier also propounded the very important concept of respiration: the disappearance of oxygen and the appearance of carbon dioxide, a phenomenon later to be associated with the concepts of gas exchange. It is agreed that the experiments of Priestly and Lavoisier, however ranked as to priority, have become to the field of respiration what Harvey's observations mean to the field of circulation.

Another important contribution to the chemistry of respiration was made by Joseph Black (1728–1799) who demonstrated that lime, when reduced to a caustic substance through burning, lost weight. This led him to question the view that lime became caustic by taking up phlogiston, and suggested that the reduced weight

was due to the loss of a specific gas or "fixed gas"—carbon dioxide

Clinical cardiopulmonary physiology was brought to the bedside by two notable contributions to physical diagnosis, the technics of percussion and auscultation Joseph Leopold Auenbrugger (1722–1809), an Austrian physician with musical talent and a fine perception of sound, first published his technic of percussion in 1761 after seven years of study He spent many years thereafter developing this technic to detect physiologic and anatomic abnormalities in the chest The technic was not well accepted until Jean-Nicholas Corvisart (1755–1821) of Paris, Professor of Medicine at the Collège de France and personal physician to Napoleon Bonaparte, translated Auenbrugger's work in 1808 and added his own experience

One of the most important figures in the history of cardiac and pulmonary disease was René-Théophile-Hyacinthe Laennec (1781–1826) Laënnec was born in lower Brittany and studied medicine at Nantes and later at L'Ecole de Médecine in Paris where he became a student of Corvisart Laennec's contributions to clinical medicine include his anatomic description of mitral stenosis in 1802 and of peritonitis in 1803, and his recognition in 1804 that phthisis was tuberculosis of the lungs His greatest contribution, however, was his discovery of the method of auscultation and invention of the stethoscope, a monaural wooden cylinder His publication in 1819, *Traité de l'auscultation médiate*, is one of the classics of medical literature in which normal and abnormal sounds in the chest are described and interpreted in relation to pathophysiologic disturbances in the heart and lungs

The mid-nineteenth century brought forth the earliest comprehensive formulation of the pulmonary volumina and their significance, reported by John Hutchinson (1811–1861) to the Medical and Chirurgical Society of London in 1846 Hutchinson clearly described and discussed the "residual air," the "reserve air," the "breathing air," the "complemental air" and the "vital capacity" and their functional significance This investigator devised the spirometer and with it measured the vital capacity in over 2000 healthy males, 26 "girls," and 360 "diseased cases" Hutchinson correctly related the vital capacity to age, physical characteristics, and to disease Despite the importance of Hutchinson's work to clinical physiology he has been largely unheralded in medical history. So it was with two other midnineteenth century investigators Heinrich Gustav Magnus (1802–1870), who in 1837 made the first quantitative analysis of blood gases showing relative amounts of oxygen and carbon dioxide in arterial and venous blood, and Lothar Meyer (1830–1895), who in 1857 showed that oxygen is bound to blood in relation to atmospheric pressure Somewhat better known in this same field was the work of Paul Bert (1833–1886), who in 1878 published fundamental studies relating oxygen tension to physiologic processes, correctly ascribing the symptoms of mountain sickness to low oxygen tension of the inspired air The next great advance in this field was the evidence presented in 1905 by John Scott Haldane (1860–1936) and John Gillies Priestley (1880–1941) that the carbon dioxide tension of the blood served as the normal stimulus of the respiratory center They further used this hypothesis to explain the hyperpnea resulting from muscular work and the apnea of forced breathing Yandell Henderson (1873–1944) extended these observations and emphasized the importance of carbon dioxide in maintaining physiologic equilibria

Outstanding contributions to our knowledge of gas transport by the blood were made by Joseph Barcroft (1872–1947), Professor of Physiology at Cambridge, who contributed greatly to our understanding of oxygen dissociation curves and to the physiologic effects of altitude Barcroft strongly maintained the belief that pulmonary alveolar gas exchange represented the simple process of diffusion

Few, if any, men have contributed more significantly to cardiopulmonary physiology during the past 50 years than Donald Dexter Van Slyke (1883–) whose analytic methods have been of key importance in oxygen and carbon dioxide physiology, lung volume and ventilation and blood flow

The contributions of the past 50 years to pulmonary physiology have been so numerous that

only passing mention of some of these is possible. Hermannsen, in 1933, introduced the maximum breathing capacity, and Tiffeneau and Pinelli, in 1948, pointed out the importance of the time-volume relationship in the performance of the vital capacity. The comprehensive work of W. S. Miller on the minute anatomy of the lung certainly deserves mention, as does the development of the bronchoscope by Chevalier Jackson and Jackson, and McCrae's observations on the mechanism of atelectasis.

During the past 30 years several centers deserve mention not only for their outstanding research but because of their training of investigators in this field. These include, the University of Rochester Lung Station, with McCann, Kaltreider, Hurtado and others, the Department of Physiology at the University of Rochester, with Fenn, Rahn and Otis, the Columbia-Bellevue Cardiopulmonary Laboratory, with Cournand, Richards and many others, the University of Pennsylvania School of Medicine, with Comroe, Schmidt, and Kety, who, in turn, inspired and trained outstanding pulmonary physiologists

Preceding World War II there was an increasing interest in pulmonary physiology, diagnostically and not least in the field of thoracic surgery However, concerning technical aspects the only important links were time-honored vital capacity determinations. Gradually there evolved methods for blood gas determinations, with reliable technics for estimating the carbon dioxide combining power of the blood, tension and oxygen saturation Subsequently, direct hydrogen ion concentration studies (pH) entered into the clinical studies of disease. Following the war there was a tremendous upsurge in the elaboration of procedures, for example, methods for studying pulmonary ventilation, diffusing capacity and pulmonary circulation Cardiac catheterization and the special radiologic technics were extended with bronchography and angiocardiography. Vital capacity time-volume relationships, maximum breathing capacity, compliance, diffusion, and ventilation-blood flow ratios have further widened the concepts and applications of pulmonary physiology, perhaps above all else, leading to a closer correlation between pathology and clinical manifestations.

The contributions of pulmonary physiology have created a high peak of confidence and enthusiasm. Never before have the internist and thoracic surgeon enjoyed comparable opportunities for dealing with malformations and degenerative disease. Still, the depths are not fully explored. In contemplating future chapters on the "beginnings" of pulmonary physiology, far greater advances will be recorded, for science is riding high in the saddle, as a live and dynamic force

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Anatomy and Pathology of the Lungs as Related to Physiologic Disturbances

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THE prime function of the lung is the exchange of oxygen and carbon dioxide. This exchange is governed primarily by physical and physicochemical laws. Therefore, a close and recognizable relationship often exists between the gross structure of this organ and its basic function, and much may be learned by knowledge of this In most other organs, the prime functions are basically biochemical and a proper understanding of the relationship of structure to function usually requires more detailed study on the molecular level. The lung, however, still affords a proper site for the integration of structure and function on a much grosser level Therefore, gross alterations of the structure of the lung often give considerable insight into disturbed function.

The basic structure and function of the lung is essentially integrated around the rich, sheetlike capillary network, where the exchange of carbon dioxide and oxygen takes place. All of the anatomic features of the lung are subservient to this The tracheobronchial tree is fundamentally designed to facilitate the entrance of air from the atmosphere for rapid and uniform distribution to this capillary network and for the efficient removal of waste gases from this capillary network Thus, the lung consists of essentially two major functional units: the spongy respiratory tissue which contains the capillary network and the branching system of bronchial tubes and alveolar ducts and sacs

Except under special circumstances, man must constantly breathe whatever air is present in his immediate environment, no matter how noxious or disturbing are the contents

We are indebted to Dr. Hollis G. Boren and the Medical Illustration Department of the Veterans Administration Hospital, Houston, Texas, for FIGURES 5, 6, 7 AND 8

Both of the major lung compartments, the tracheobronchial tree and the lower respiratory portion consisting of the alveoli, are designed to provide the maximum defense against any noxious agents that may interfere with the essential function of gas exchange

Structure of Bronchi and Bronchioles

Beginning with the trachea and, extending to bronchi with lumens 1 mm. in diameter, the walls contain cartilagenous rings These rings are incomplete in order to provide a maximum degree of rigidity and yet permit the necessary expansion and narrowing of the bronchial lumen as is functionally required A certain amount of rigidity is necessary to prevent collapse of the bronchial walls against each other during the pressure alterations occurring during the ventilatory cycle or induced by transitory episodes of obstruction caused by mucus, spasm, foreign bodies, etc In the uncommon condition of bronchial chondromalacia, in which the bronchial cartilages have become unduly softened, the walls may collapse particularly during the inspiratory phase of the ventilatory cycle and interfere with the usual flow of air. The amazing extent to which a bronchial lumen may at times become obliterated, even in the presence of apparently normal bronchial cartilage, may be observed when spasm occurs during bronchoscopy.

These cartilagenous rings are incomplete posteriorly, and the gaps between the open ends, as well as the spaces between the cartilagenous rings, are filled with elastic, reticulin, collagen and smooth muscle fibers. The bundles of smooth muscle, elastic and fibrous tissue are so arranged as to enhance the elasticity of the bronchial wall

The trachea divides into two primary bronchi and these branch dichotomously to supply all portions of both lungs. The total cross sectional area of the lumens of each two branches is greater than the cross-sectional area of the lumen of the parent tube. Since the same amount of gas must ultimately pass through the parent tube as passes through the two branches with the greater cross-sectional area, the air must travel through the parent tube at a greater speed. This fact must be considered in the evaluation of ventilatory studies and auscultatory sounds during physical examination. The intrapulmonary branches of the bronchial tree, although basically similar to the trachea and main bronchi, differ in certain respects from the latter. The cartilagenous plates are more irregular in shape. Some of these irregular cartilages encircle the lumen completely. The spaces between the cartilages contain connective tissue that is continuous with the perichondrium of the cartilages. Two layers of smooth muscle completely encircle these bronchi in a spiral-like fashion wound in different directions, one clockwise and the other counterclockwise. The smooth muscle is particularly prominent in the bronchiole walls and is thicker in relation to the size of the lumen than in any other portion of the bronchial tree. It is significant that this is the main site of bronchospasm in hypersensitive or allergic states. The smooth muscle continues to the alveolar sacs, where on cross-section it appears as a small sphincter. Diffuse interlacing bundles of elastic tissue are present in the lamina propria. Again, the entire structure is so designed as to give the maximum rigidity with regard for necessary elasticity and distensibility.

The entire series of tubes to the level of the noncartilagenous bronchi or bronchioles are lined with pseudostratified and ciliated columnar epithelium that contains numerous goblet cells. This epithelium lining rests on a lamina propria that is superficially condensed to form a basement membrane. Many mucous glands are present. The secretory portions of these lie within the submucosa. Ducts from these glands pierce the elastic lamina and empty into the lumens of the air tubes. Some of the secretory units of these mucous glands even lie beyond the outer border of the smooth muscle. Lymph nodules, lymph nodes and scattered areas of lymphoid tissue are present along the outermost portions of the bronchial tubes.

Defense Mechanisms

Several structures in the tracheobronchial portion of the respiratory tract are concerned with the prevention of noxious agents or particles from interfering with the normal function of the airways. These are the cilia of the epithelial lining, the goblet cells of the mucosa, the mucous glands, the fibromuscular and elastic coat of the bronchial wall, and the reticulo-endothelial and lymphocytic cell aggregates. These structures often prevent obstruction to the normal flow of gas by removing excessive secretions, bacteria, foreign particles and inflammatory exudate. Perhaps the single most important structure in this regard are the cilia. Numerous studies on excised mucosal strips have demonstrated the remarkable efficiency of these cilia. It has been estimated that cilia can move a particle of carbon encased in mucous along the epithelial surface at the rate of 3 cm. a minute. The ability of the cilia to function properly may be modified by changes in temperature, moisture, chemical environment and acute or chronic inflammatory conditions. Inhibition of normal ciliary activity may seriously impair the cleansing mechanism of the lung. In portions of the tracheobronchial tree in which the normal pseudostratified ciliated epithelium has been anatomically altered or replaced by metaplastic or nonciliated epithelium, there is a predisposition toward the development of repeated infection as well as delayed resolution of inflammation.

Acting in conjunction with this ciliary activity is the mucus material secreted by the bronchial mucus glands and the goblet cells. The mucus coats foreign particles, bacteria, etc., and thus enables the cilia to remove these particles with an increased efficiency. Alterations in the viscosity and quantity of mucus secretion may interfere with the ability of the cilia to remove foreign material. Although produced primarily as a defense mechanism in response to irritants, alterations in the nature of the mucus may make it sufficiently viscid

and tenacious so as to interfere not only with the ability of the lung to rid itself of noxious agents but also with the basic function of the passage of gas in and out of the lung. The mucus itself may produce obstruction. Excessive secretion of mucus may favor the spread of infectious agents to other areas of the lung. In cystic disease of the pancreas, otherwise known as mucoviscidosis, there is an abnormally viscid type of mucus secreted in the lung. As a consequence of the bronchial obstruction, lung suppuration, bronchiectasis and emphysema are the usual sequelae in this condition. In certain forms of chronic bronchitis seen most frequently in England, changes in the quantity and quality of the mucus occur. This leads to significant impairment of lung function. In this form of bronchitis, the production of copious amounts of mucus is reflected anatomically in marked hypertrophy of the bronchial mucus glands. Enlargement of the gland ducts may at times be of such proportion as to appear as diverticuli in bronchographic studies. At present there is inconclusive evidence that the normal mucus contains substances that prevent viruses from combining with the respiratory epithelial cells.

The muscular layer of the bronchial wall is innervated by both parasympathetic and sympathetic fibers. Under appropriate stimulation, alterations in the dimensions of the bronchial lumina may occur, as well as upward and outward peristalsis of the bronchial wall. Alterations in the lumen size, along with peristalsis, undoubtedly contribute to the expulsion of the mucoid secretions, inflammatory exudates and other foreign material that may be present in the lung.

The lymphoid and reticulo-endothelial cell aggregates serve as a source for scavenger cells that phagocytize bacteria and other particles. These scavenger cells are found in the interstitial tissues and within the alveolar spaces and the lumina of the smaller bronchi. These cells may carry the phagocytized material to the nearest lymphocytic cell collection and thence into the lymphatic circulation, or else may be swept out of the lung by the ciliary activity of the respiratory epithelium. More recently it has been claimed that the epithelial cells lining the alveoli proliferate in response to various irritants and engulf these irritants. This is in accord with the concept that the alveolar lining cell is multi-potential. These masses of cells are seen most frequently in chronic inflammatory conditions. These collections have been previously mistaken for perivascular-intralymphatic groups of macrophages, whereas in reality they are intra-alveolar.

In addition to the structural elements, several reflexes are involved in the protection and cleansing of the lung. These are the sneeze, gag and cough reflexes. Partial inhibition or total paralysis of these may impair lung function. Interference with the gag reflex may permit the entrance of pathogenic bacteria, necrotic debris, food particles or other foreign material into the lower respiratory tract. In many cases of aspiration lung abscess, the gag reflex has been, at least temporarily, impaired. Such situations as alcoholic stupor, the anesthetized state or central nervous system disorders may depress the normal activity of the gag reflex. The effectiveness of the cough reflex as a defense mechanism is dependent on an intact chest cage and neuromuscular apparatus, and is aided by the presence of collateral ventilation. Insufficient or altered mucus as seen in hypovitaminosis A may seriously interfere with the efficacy of cough. Excessive and ineffective cough can become quite harmful to debilitated and elderly individuals. The efficiency of the total array of defense mechanisms is attested to by the fact that usually only particulate matter, less than 10 microns in diameter, can penetrate to the alveolus, which is approximately 250 microns in diameter.

Terminal Ventilatory Units

The parenchyma of the lung, in which the respiratory function takes place, is divided into various anatomic units and subunits. Distinction is made between the anatomic lobule and that microscopic unit of lung structure originally described by Miller[13] as the primary lobule. The primary lobule consists of an alveolar duct with its atria, saccules and associated alveoli. The anatomic lobule is that area of lung parenchyma supplied by one bronchiole, and is often referred to as the secondary lobule since

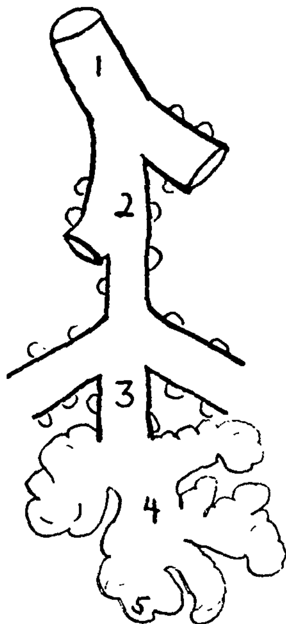


FIG 1 —The terminal ventilatory unit (schematic and not according to relative size) 1 Bronchiole, 2 Respiratory bronchiole, 3. Alveolar Duct, 4 Alveolar Sac, 5 Alveolus

it is larger than and contains from 10 to 15 primary lobules Reference to it as a secondary lobule is often confusing. In the same manner, tertiary lobules contain many secondary lobules The base of the secondary lobule is usually directed toward the pleural surface, with its apex at the point of entrance of the supplying bronchiole. These lobules are irregular in size and shape and the bases vary in size from 1 to 2 cm. in diameter. Some of the bases of the lobules face towards the interior of the lung. The final branches of the intralobular bronchioles are the respiratory bronchioles It is the unit of lung related to this terminal single respiratory bronchiole that was classified by Miller[13] as the primary lobule. This is the smallest functioning anatomic unit of lung tissue. The respiratory bronchioles terminate in a spongy network of respiratory tissue consisting of alveolar sacs, the walls of which contain rich capillary networks It is at this point that gas exchange takes place (FIG 1).

Where the bases of the secondary lobules are in direct contact with the pleura, the septal extensions of the visceral pleura enclose these lobules. A similar situation is present in the pig where the lobules are clearly separated by prominent fibrous septa In the dog and rabbit, the lobules are not clearly separated from each other. Comparative anatomic studies of the lungs in various species of animals have shown that considerable variation in lung structure exists among the various species In addition to septal variations, there are differences in the rigidity and dimensions of the bronchial tree and in significant details of the vasculature In many respects the anatomy of the pig's lung is more similar to man than are the lungs of the rat, rabbit, cat and dog Consideration must be given to these differences when correlations are made with experimental findings regarding the pathogenesis of human pulmonary disease [12]

The alveolar wall with its interface has already been mentioned as the all-important site of gas exchange These walls separate the alveoli from one another and contain apertures commonly referred to as Kohn's pores The significance of these apertures will be discussed later.

The alveolar ducts open into the alveolar sacs and these sacs appear as shallow bowls This arrangement favors aeration. In the deflated state, which corresponds to the terminal phase of the expiratory portion of the ventilatory cycle, the alveoli are apparently cup-shaped. Upon distention, this cuplike shape changes into a saucer shape. Distention takes place from the intrathoracic portion of the trachea down to the alveolar sacs. The main site of volume change in the peripheral portion of

this system, however, is not the alveolar sac but, rather, the space or alveolar duct around which the alveoli are arranged.

The Interalveolar Wall

The structure of the interalveolar wall has been a matter of controversy for some time. Chief among the unsettled questions was the nature of the lining of the interalveolar wall. The existence in the adult human lung of a continuous alveolar epithelial lining had remained unproven. Prominent epithelial linings have been frequently noted in diseased adult lungs. However, it was thought by some that the lining seen in the diseased lung could have originated as a downgrowth from the epithelium of the terminal air passages. Studies of lung tissue with the electron microscope have provided the most convincing support for the presence of such a continuous lining in the adult human lung. Low,[10] who has made some of the original electron microscopic studies of the structure of the lung, found that in the rabbit, guinea pig, dog and man, this attenuated epithelium has an average thickness of 0.2 micron. In these studies, it has also been demonstrated that at least four structures are interposed in this area between the alveolar space and the lumen of the capillary. These are the capillary endothelium, its adjacent basement membrane, another basement membrane and the alveolar epithelium. This continuous, attenuated epithelium is of endodermal origin. The thicker portion of the cell consists of a nucleus that may be seen with the ordinary light microscope. Previously, this portion of the cell has been called septal cell or epicyte. This continuous epithelial layer appears to contain elastic properties. It is estimated that its total surface area ranges between 75 and 100 M^2. Within the alveolar wall between the two basement membranes is a tissue space containing elastic, reticulin and collagen fibers embedded in a matrix of ground substance consisting of mucopolysaccharides. As will be subsequently discussed, alterations in the nature and quantity of any of these elements in the interalveolar wall may significantly interfere with the exchange of carbon dioxide and oxygen and with the perfusion of blood through the capillaries (Fig. 2).[5, 10]

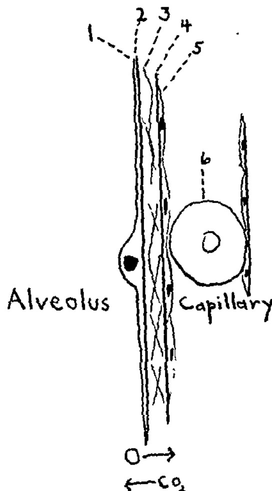


Fig. 2.—The components of the interalveolar wall (schematic and not according to relative size). 1. Attenuated alveolar epithelium. 2. Alveolar basement membrane. 3. Ground substance containing reticulin

Elastic Tissue of Lung

The elastic properties of the lung that are directly related to its compliance and resistance are dependent to a great extent on the pattern of arrangement of elastic fibers, as well as such other tissue elements as reticulin and collagen. Changes in the character of the surface tension on the alveolar interface may likewise have considerable bearing on elasticity, compliance and resistance.

Loosli's studies[9] on the development of the

elastic tissue of the lung from prenatal to adult life may clarify some problems concerned with lung compliance In the 5 month old fetus, elastic fibers are present and fairly well developed in the pleura, blood vessels and bronchial walls As the lung begins to lose its glandular configuration and potential air-containing channels appear, elastic fibers are noted in tissue at points of entrance into these channels. At birth, the elastic fibers are seen only at the mouths of the alveoli. Elastic fibers increase in amount, but until the age of 5, these are still present only in the area of the openings of the mouths of the alveoli At the age of 12 years, the elastic fiber system is still incomplete in the walls of the alveoli and the alveolar ducts At the age of 18, it appears complete This probably represents completion of lung growth This late development of the elastic fiber system in the alveolar walls is probably essential to allow for completion of lung growth wherein the alveolar ducts, saccules and alveoli increase in length and size This also would seem to indicate that, at least until the time lung growth is complete, a fully formed elastic fiber system is not essential for normal functioning of the lung [9]

Considerable emphasis has been placed in recent years on alterations in the elastic tissue framework of the lung as the prime defect in the pathogenesis of emphysema. Histochemical studies on the amount of elastin present in the normal lung at different ages and in diseased lungs have yielded conflicting results This is understandable because in such an air-containing structure as the lung, relative proportions of different substances may vary in concentration to each other In such a condition as emphysema, increased proportions of elastic tissue from bronchial walls and blood vessels may alter the situation. In addition, in diseased states there may be increases in collagen fibers and smooth muscle. This also alters the relative proportions of elastic tissue to other substances Further, it is known that under certain pathologic conditions there may be an increase in the number of elastic fibers, such as is seen in the blood vessel walls in the hypertensive state, in fibroelastosis of the endocardium associated with congenital defects of the heart and in the fibrosis of liver cirrhosis. Likewise, in such a condition as emphysema where there may be increased intra-alveolar pressure with resultant stress on the surrounding elastic tissue, an increase in elastic fiber content may result. Stress on the elastic tissue can conceivably alter the alignment of its protein linkages and alter the physical and chemical makeup of these fibers. This might reflect itself in an altered tinctorial quality of this tissue [14]

The intricate relations of the various elastic fiber systems of the lung to each other and to the reticulin and collagen fiber systems so connect all structures of the lung to each other that focal alteration at any one point must of necessity reflect on the function of other related adjacent areas Disturbance of traction subsequent to elastic tissue destruction at one site may interfere with the ability of nearby bronchi to remain patent during the expiratory phase of the ventilatory cycle It must again be emphasized that in addition to the elastic fiber system, reticulin fibers, collagen fibers, pulmonary blood vessels and the alveolar epithelium contribute to the elasticity of the lung

Collateral Ventilation

Kohn's pores are openings in the alveolar walls These apertures in the alveolar walls are approximately 10 microns in diameter and are large enough to permit passage of the particulate matter that has entered the alveoli from the bronchioles This can be clearly demonstrated in inflamed lungs where fibrin threads may be seen extending through these pores into adjacent alveoli. Aside from serving as pathways whereby transudates, exudates, cells and organisms may spread, these serve as a means for collateral ventilation.

Collateral ventilation is the means whereby aeration of the lungs is maintained in the presence of temporary or more permanent occlusion of the smaller bronchioles by exudates, transudates and foreign material. It also enables enough air pressure to be established in the parenchyma distal to the blocked bronchioles to permit effective cough. Collateral ventilation thus limits the degree of atelectasis or edema that might constantly be developing In emphysema, Kohn's pores may serve as a path-

way for the escape of trapped air and prevent further elevation of intra-alveolar pressure. However, it should also be understood that some investigators into the pathogenetic mechanisms involved in the development of emphysema implicate collateral ventilation as the means whereby air becomes entrapped behind or distal to a blocked bronchiolus. The more recently described bronchoalveolar communications of Lambert may also serve as bypasses above obstructed bronchioles to more distally located alveoli (FIGS. 3 AND 4).[6, 20]

LYMPHATICS

The lymphatic system of the lung contains thin-walled lymphatic vessels which extend as far as the alveoli The interalveolar walls do not contain definitive lymphatic channels This may partially account for the rapidity with which pulmonary edema may develop The usual direction of flow in the lymphatic vessels is toward the hilar region along the bronchi and pulmonary arteries. The direction of flow in the most peripheral portions of the lung and the pleura is along the pulmonary vein toward the hilar nodes Unusual degrees of air space distention may conceivably obstruct lymph flow, with the subsequent appearance of edema and distended, extremely thin-walled collateral lymph channels Extensive deposits of tumor cells at the hilar region may block lymph flow. When this occurs, retrograde permeation of tumor cells along these lymph channels may take place.

BLOOD SUPPLY

The lung is supplied by an independent arterial system (the lesser circulation), as well as by branches from the systemic circulation. The significant functional circulation is the separate pulmonary arterial system Under certain conditions of disease, where there is alteration in the rate of flow in the pulmonary arterial system or where there is considerable granulation tissue formed, the bronchial arteries may become stimulated to expand, with the production of obvious communications between the two circulations Ordinarily, in the anatomically unaltered lung, anastomotic or collateral channels are not easily demonstrable[8]

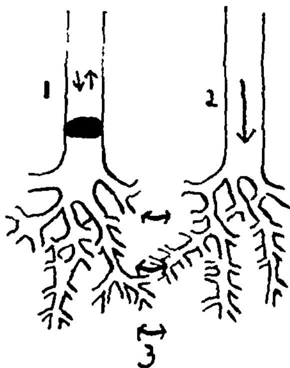


FIG 3—Schematic illustration of collateral ventilation in the presence of an obstructed bronchiolus.



FIG 4—Bronchiole with arrows pointing to a canal of Lambert (bronchiole-alveolar communication).

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lungs removed and allowed to float in a pan of fixative It is desirable to tie off the blood vessels before the lungs are removed. With this method, whole sections, according to the techniques of Gough[4] and others, may be made, as well as small, thin or thick sections for routine and special staining. Such methods as fume fixation, special injection studies of the vasculature or three-dimensional studies under the dissecting microscope should be performed as the situation requires. Undoubtedly, many of the conflicting findings and interpretations of the pathogenesis of various diseases are caused by variations in methods of preparation of the pulmonary tissue for both macroscopic and microscopic study.

The fume fixation technic with the application of newer stains as developed and utilized by Blumenthal and Boren[1] may prove to be an excellent method for further clarification of structural alterations of the lungs in various disease states. This method provides a means for studying whole lungs in greater detail and yet retains the three dimensions Unstained whole lung sections prepared by fume fixation provide excellent contrast between the gross structure of the normal lung (Fig. 5) and the lung with extensive pulmonary emphysema (Fig 6). Such lung sections viewed with low magnification (15x) further delineate the terminal air space structure in the normal lung (Fig 7) and in pulmonary emphysema (Fig. 8)

Pathogenesis of Disease

In the consideration of the pathogenesis of disease, it must be recognized that the lung parenchyma has only a limited capacity to respond to injury, and a variety of mechanisms may produce alterations which terminate in similar anatomic pictures This fact is well paralleled in the kidney and liver. In the kidney, hypertensive disease associated with vascular change, bacterial inflammatory disease such as chronic pyelonephritis, and hypersensitivity diseases as manifested by glomerulonephritis, may all produce end stage appearances that are essentially similar In the liver, biliary cirrhosis secondary to obstruction and ascending infection, cirrhosis secondary to nutritional disturbances, and necrosis secondary to viral hepatitis may all terminate in forms of cirrhosis that cannot be clearly separated from each other. Thus, in considering diseases of the lungs, whether they be interstitial inflammation and fibrosis or emphysema, consideration must be given to the fact that many different mechanisms may be responsible for these alterations

It is frequently noted that the severity and character of the clinical disability and the type and degree of functional impairment cannot always be quantitatively correlated with the amount of lung tissue involved as demonstrated either on the x-ray picture or the actual specimen. If, however, the site (such as pleura, bronchi, alveolar wall, etc) of anatomic alteration is also considered, then a more rational relationship between altered structure and function becomes evident [17]

In general, and from a schematic point of view, the following areas of change correspond to particular patterns of dysfunction. Constricting forms of pleural disease usually impair ventilation and possibly perfusion Changes in the components of the interalveolar wall are reflected in disturbances in diffusion. Disease of the bronchioles, alveolar ducts and



Fig 5—Unstained saggital section of normal whole lung The smallest visible openings are alveolar ducts and alveolar sacs

The structure of adult pulmonary arteries and arterioles is in complete accord with the fact that the pulmonary circuit is a low pressure and low resistance system. Several characteristics of the pulmonary vascular bed distinguish it from the systemic arterial system. These are its distensibility potential, its large reserve, and the relative lack of musculature in the smaller arteries and arterioles. These low resistance factors are of importance in evaluating the diverse effects of disease on the pulmonary vascular bed The major pulmonary vessels which extend along the cartilagenous bronchi are primarily elastic arteries From these elastic arteries arise the muscular arteries which vary in diameter from 100 to 1,000 microns. These vessels, in comparison to their counterpart on the systemic side, contain very little muscle. The muscular arteries extend along the bronchioles and alveolar ducts The 100 microns sized muscular arteries give rise to arterioles. The proximal portions of these arterioles are similar in structure to the muscular arteries from which they arise, but soon lose their entire muscular coat The capillary network is derived from the nonmuscular arterioles The rich capillary bed in the interalveolar walls is in close contact with the alveolar interface Under usual physiologic conditions, the diameter of these capillaries is no greater than the diameter of one red blood cell In this way, the maximum exposure of each red blood cell is assured for the purposes of gas exchange [2]

The pulmonary venules are similar in appearance to the nonmuscular segments of the arterioles, and differentiation under ordinary circumstances is quite difficult These pulmonary venules coalesce to form larger venous trunks which contain irregularly distributed muscle bundles in their walls, in contrast to the orderly arrangement of smooth muscle in the pulmonary arteries.

Pleura

The visceral pleura is a fibroelastic membrane covered by a layer of flat mesothelial cells This in turn is coated with a thin film of fluid that lubricates movements of the visceral over the parietal pleura. The pleural space under normal conditions is actually air-tight and is in reality only a potential space. The intimal surface of the visceral pleura is intimately bound to the underlying lung parenchyma by extensions of fibroelastic septa. A relatively large amount of elastin is present in the visceral pleura and is, to a great extent, responsible for considerable elastic recoil of the constantly stretched lungs.

Patterns of Disease

Diseased states may involve primarily the pleura, the bronchial airways at various levels, the alveolar sacs and alveoli, the interalveolar walls, the vascular bed or the lymphatic system It would be unusual for any particular disease to confine its effects entirely to any one of these portions of the lung, but the alterations in any one of these areas may be so extensive and predominating as to produce the characteristic clinical or functional disturbance reflecting these changes It must also be remembered that, because each portion of the lung is structurally so intimately related to other portions, involvement of one area must of necessity disturb other regions.

Preparation of Pulmonary Tissue

The ability to relate anatomic alterations to functional disturbances and pathogenesis of disease correctly is, to a great extent, dependent upon the methodology used in preparing the tissue for study.

Because of the nature of its air-containing function, the structure of the lung is delicate and is therefore peculiarly susceptible to distortion and the production of artifacts in its preparation for study. Fixatives, dehydrating agents, cutting, the state of distention and handling may considerably alter the structure For the proper study of the lungs, particularly where the pathogenesis of disease is in question and where correlation with the physiologic studies obtained during life is desired, it is important for the lungs to be prepared with a certain minimum of care and standardization of procedures Preferably, the lungs should be fixed in situ with the cannula inserted into the trachea. The fixative should flow in under low pressure until the lungs show their usual contours. The trachea should then be tied and the



Fig 8 —Unstained section of pulmonary emphysema demonstrating extensive tissue destruction with its consequent departitioning of space The strandlike remnants of tissue are largely of arteriolar origin (magnification 15×)



Fig 9 —Small bronchus with marked increase in thickness of muscular layer in case of asthma with emphysema.

vascular disease or from the effects of associated systemic or pulmonary disease. The former is rare while the latter is common.

The structural alterations in the pulmonary vascular bed produced by primary lung disease are of clinical and physiologic significance only if they alter the perfusion of the ventilated lung, increase the pulmonary vascular resistance or enhance the development or enlargement of various bronchopulmonary communications or shunts The most consistent and prominent morphologic changes in the pulmonary vascular bed are actually secondary manifestations of the alterations in blood flow, volume, and tension produced by disease of the lungs These changes consist basically of atherosclerosis in the larger elastic arteries, hypertrophy or at least apparent thickening of the muscular arteries and fibrosis of the intima in the smaller arteries and precapillary arterioles Other secondary changes may at times also



Fig 10 —Bronchiolus with ulceration of mucosa and chronic inflammation of wall in advanced emphysema

sacs produce airway obstruction and irregular distribution of gas. Vascular involvement alters perfusion and may terminate in pulmonary *hypertension Again, it must be emphasized* that involvement of one type of necessity must influence the structure and function of other areas.

Emphysema

Undoubtedly the most frequent, important and disabling alteration in the lung that affects ventilation is overdistention of the pulmonary parenchyma This overdistention is generally referred to as emphysema Emphysema is a catch-all term that undoubtedly represents the *end stage and irreversable picture of different* disease entities It is frequently a secondary but important consequence of tuberculosis, bronchiectasis and silicosis. Currently it is more often observed without any obvious underlying disease or clearly identifiable pathogenesis. In England, it appears to be a common complication of their particular type of chronic bronchitis. It is variously referred to as large lung, idiopathic or obstructive emphysema

Such pathogenetic factors as traction *secondary to atelectasis, fibrosis and surgical* obliteration of lung tissue and enlargement of the thorax, obstruction of air passages by mucus, spasm, muscle hypertrophy (Fig. 9), fibrosis of bronchioles, distortion by enlarging bullae and loss of tractional support of bronchioles, destruction of lung tissue by necrosis (Fig. 10), atrophy or tension, and, finally, alteration of elasticity, may singly or in various combinations, produce emphysema of the lungs [3, 7] These mechanisms may produce focal, single, irregular, diffuse or centrolobular areas of distention (Figs 6, 8, 11 and 12). Discussion of the relative importance and validity of the different pathogenetic factors is beyond the scope of this chapter [11, 19]

Alterations in the Pulmonary Vasculature

Pathologic changes in the pulmonary vascular bed may result from primary or intrinsic



Fig. 6 —Unstained horizontal section of whole lung showing the irregular distribution of advanced emphysema.



Fig 7.—Unstained section of normal lung demonstrating relative uniformity of terminal air space structure (magnification 15x).

3. Those in which the interstitial changes are secondary to basic disturbances in the lungs, such as chronic pulmonary congestion with or without superimposed secondary infection. Examples of this would be the alveolar wall thickening in chronic pulmonary congestion, particularly that secondary to mitral stenosis Recent evidence, however, tends to minimize the role of congestion secondary to mitral stenosis as a pathogenetic mechanism whereby alveolar wall fibrosis may develop. Another example would be the fibrosis of the lungs that has been observed with hexamethonium therapy for essential hypertension. Recently it has been postulated that the methonium salts produce pulmonary fibrosis not as a result of congestion but because these salts are directly irritating to the lungs.

4. Those in which a specific acute infection can be identified, such as the atypical pneumonias These are generally regarded to be viral in origin A specific viral pneumonia of this type would be psittacosis

5 Finally, there are the cases of indeterminate diffuse inflammation and fibrosis in which no etiologic mechanism is demonstrable. These often have an insidious onset and demonstrate varied but usually relentlessly progressive courses.

These indeterminate interstitial fibroses do not necessarily follow the pattern and course described by Hamman and Rich These investigators delineated a rather precise clinical-pathologic syndrome that perhaps began with a vague upper respiratory picture and usually terminated fatally within a matter of a few months either from the pulmonary or cardiopulmonary insufficiency. Interstitial fibrosis of the lungs does not necessarily follow this course. Some cases may progress rapidly, while in others the lesions may develop slowly over a period of a year or two, and in still others the disease may persist for five years or longer The histologic alterations in the alveolar walls vary with the duration and intensity of the process so that in those of short duration there is a greater degree of inflammation relative to the fibrosis Those lasting a year or so will have more fibrosis, and those extending over many years reveal alveolar walls with considerable amounts of well developed collagen



Fig 15 —Diffuse interstitial (interalveolar wall) fibrosis The alveolar epithelial lining is quite prominent.



Fig. 16 —Granulomatous lesion (case of hematogenous miliary tuberculosis) in the interalveolar wall



FIG 14—Angiomatoid or plexiform vascular lesion in the lung seen in association with severe chronic pulmonary hypertension (probably evolves from dilatation of a pulmonary arteriole)

poventilation syndrome. As these conditions advance, pulmonary hypertension develops which may be severe enough to produce cor pulmonale, yet in some cases of kyphoscoliosis, as well as unilateral thoracoplasty, the emphysema and the structural changes in the blood vessels are entirely inadequate to account for the cor pulmonale. In the alveolar hypoventilation syndrome, there is no emphysema or notable primary structural alterations in the pulmonary vascular bed. Such conditions suggest that such factors as hypoxia and hypervolemia may be primary in the development of pulmonary hypertension and that the structural alterations develop later. In kyphoscoliosis and unilateral thoracoplasty, unilateral kinking of vessels is probably not a factor because the secondary vascular manifestations of pulmonary hypertension are equally reflected in both lungs.

Direct structural involvement of the pulmonary arterial system with thrombi, embolic carcinoma, polyarteritis and schistosomiasis requires no comment as to the obvious increase in vascular resistance observed In these conditions, plexiform vascular arrangements have been demonstrated which are similar to those noted in the pulmonary hypertension of congenital cardiovascular disease Whether these plexiform vascular arrangements are by-passes, vascularized granulation tissue or shunts is not always clear (FIG. 14).

Distinction must be made between those *primary structural alterations in the pulmonary* vascular bed produced by lung disease and those alterations secondary to the development of pulmonary hypertension Close correlations are not always apparent between the extent of morphologic vascular change and the degree of cor pulmonale Observations of a variety of pulmonary diseases suggest that functional factors are of greater significance than anatomic alterations in the earlier stages of pulmonary hypertension

INTERALVEOLAR WALL DISEASE

Fibrin adherent to the surface of the alveolar walls, increased prominence and proliferation of the alveolar lining cells, increase or change in the structure of interalveolar wall *reticulin*, collagen or elastic tissue may interfere with the diffusion of oxygen, as will congestion, exudate and edema. There appears to be an *increasing* group of diseases that produce abnormalities of the interalveolar walls.

Diffuse forms of interstitial inflammation and/or fibrosis of the lungs may be divided into several broad groupings

1 Those in which the agents causing the interstitial alterations are clearly known and at times demonstrable, or those in which the alterations are specifically related to a definite disease syndrome. In this category, one might include berylliosis, Boeck's sarcoid, hematogenous miliary tuberculosis, atypical forms of *lipid pneumonia, toxoplasmic* pneumonia, rickettsial pneumonia and radiation pneumonitis

2 Those in which the interstitial changes are associated directly or indirectly with some definite disease entity, such as scleroderma, lupus erythematosus and perhaps rheumatoid disease In these situations the damaged lungs reveal no histologic changes that are *specifically* related to the basic or associated systemic disease process Hypersensitivity and auto-immune mechanisms may be important.

Normal Respiratory Physiology

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The Regulation of Breathing

Introduction

THE primary objective of respiration is to supply the alveolar air, and consequently the blood and tissues, with oxygen and to eliminate carbon dioxide Although normal breathing is, to a certain extent, under voluntary control it is essentially an involuntary act. Man for the most part is not conscious of his rate and depth of breathing

Before entering into a discussion of the regulation of ventilation, certain facts generally agreed upon should be mentioned (1) CO_2 added to the inspired air up to a concentration of 10 per cent will cause an increase in ventilation Slight changes in the P_{CO_2} evoke a response. Breathing 3 per cent CO_2 will double ventilation, 5 per cent will quadruple ventilation The maximal ventilatory effect that can be expected from CO_2 inhalation is in the neighborhood of 60 to 90 L. per minute. An inspired CO_2 over 10 per cent or a P_{CO_2} of 65 mm Hg may reduce the respiratory volume and even have an anesthetic effect (Fig 1A and 1B). (2) Voluntary forced breathing results in hyperventilation, with a lowered P_{CO_2} followed by apnea until the P_{CO_2} restores itself to normal levels (40 mm. Hg). (3) Acute hypoxic hypoxia (an inspired O_2 of 12 per cent) results in an increase in ventilation When breathing a higher concentration of oxygen the ventilation remains essentially the same as with breathing air. (4) Exercise and muscular activity increase O_2 consumption and CO_2 production, with a resultant increase in ventilation This increase in ventilation occurs in spite of the fact that the alveolar and the arterial P_{O_2} and P_{CO_2} remain within the normal range Actually, during heavy work the P_{CO_2} is usually lower and the P_{O_2} higher than that found at rest. (5) Changes in the pH of the blood cause changes in the ventilation. A rise in the blood pH above 7.4 will decrease ventilation, a decrease in pH below 7.4 results in an increase in ventilation When acids are added to the blood, ventilation increases. (6) Drugs such as morphine, sedatives, anesthetics and chlorpromazine will decrease ventilation. Others such as stimulants and salicylates may actually increase ventilation.

Nervous Control

The afferent nervous impulses and stimuli affecting ventilation have been shown in animals to be located in the region of the floor of the fourth ventricle of the medulla, caudal to the entrance of the eighth cranial nerve and extending to the level of the inferior olivary nucleus. It appears that in the regions of the medial and lateral reticular formation, most of the integration of stimuli takes place. The respiratory center has two main areas of activity. An inspiratory center in the ventrocaudal part of the reticular formation and an expiratory center in the dorsocranial area. Activity of these centers has been stated to be either inhibitory or facilitatory. Higher centers, the pneumotaxic, in the pons or the cortex are probably responsible for the spontaneous rhythmicity which occurs. Fibers transmitting impulses from stretch receptors of the lungs and other respiratory reflexes enter the brain stem through the cranial fibers of the vagus and emerge in the solitary tract passing to different areas, one with expiratory and one with inspiratory action, both having low excitation thresholds Other neurologic connections of unknown significance exist The vagus pathway is chiefly one of curtailing the inspiratory action (Fig 2) Hess interprets the action of the vagus as chiefly a tonic innervation to the respiratory

and only scant evidence of inflammation (FIG. 15). Regardless of the duration of these cases it is difficult to determine the etiology.

In the nonspecific and specific interstitial fibroses, such as berylliosis and sarcoid, the blood vessels throughout the lung are encased in an environment of fibrosis, inflammation, granulation tissue and edema (FIG. 16). This undoubtedly reduces the distensibility of the entire vascular bed. The alveolar-capillary block and diminished ventilation of the lung in these conditions contributes important functional disturbances that hasten the onset of pulmonary hypertension [18]

PARENCHYMAL (INTRA-ALVEOLAR) FIBROSIS

This form of fibrosis, in which there is complete obliteration or necrosis of parenchyma or organization of exudate within the alveolar spaces, is perhaps one of the most frequent forms of pathologic change in lung tissue It may be focal, localized, massive or diffuse The changes obliterate or involve the associated alveolar walls, bronchi and blood vessels Organization of unresolved bacterial pneumonias, tuberculous pneumonia, necrosis and ulceration, lipoid pneumonias, the nodular fibrosis of anthracosilicosis are diseases producing this pattern of change Involvement of the particular area of pulmonary parenchyma is such that it is no longer a functioning unit. A secondary change in neighboring tissue or the contralateral lung may be anatomic, compensatory distention emphysema Functional disturbances are usually directly proportional to the amount of lung tissue primarily involved and the degree of secondary change in the neighboring lung. In a sense, the disturbance is analogous to some of the changes one might expect to find following surgical removal of varying portions of lung tissue Since the lung has considerable reserve, the functional changes that do occur are more often related to the associated secondary change in the remaining and functioning lung parenchyma

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concept holds that the main control of ventilation lies in the medulla and the respiratory center and the chemoreceptors come into action as emergency mechanisms Hypoxia may depress the center, making it unresponsive to the usual chemical stimuli, thereby allowing the chemoreceptors to dominate. Another concept suggests that there is normally a combined effect of direct stimulation of the center and a reflex stimulation by way of the chemoreceptors The nervous supply to the chemoreceptors consists of a branch of the glossopharyngeal nerve of Hering and a depressor nerve which joins the vagus Hypoxia is considered to be the primary stimulus for these peripheral chemoreceptors

Chemical Stimuli

Changes in CO_2 tension of the arterial blood result in a corresponding change in arterial pH. Because of these associated responses, it is difficult to determine whether CO_2 or pH is the principal chemical stimulus in the control of breathing Changes in pH from CO_2 cause a greater change in ventilation than an equal change in pH resulting by other means It may be that the arterial blood findings do not reflect the true state of the cells of the respiratory center. Increased ventilation can be produced by a low pH and a low P_{CO_2} such as occurs in diabetic acidosis and renal acidosis. Increased ventilation may also occur with a normal pH and a high P_{CO_2} The Gray dissociation or multiple factor theory states that there is an additive relationship among the three stimuli, P_{O_2}, pH and P_{CO_2} This theory applies to the resting state when it is presumed that ventilation is under chemical control It does not explain, however, the increase in ventilation which occurs with exercise where the arterial pH and CO_2 may be normal or even lower than normal

The mechanism of respiratory control during hypoxia is poorly understood It is of extreme importance during anesthesia, and in emphysema with CO_2 retention The low oxygen stimulus acts chiefly on the accessory vasomotor respiratory center and on the carotid and aortic bodies Abolishment of this hypoxic drive by pure oxygen administration may lead to CO_2 retention and narcosis At high altitudes hypoxia leads to hyperventilation; the hypoxic stimulus is apparently a stronger one than the hypocapnic response since hyperventilation continues.

Gas Exchange

The exchange of gas between the atmosphere and the pulmonary capillary bed involves extensive, complex physical and physiochemical processes. The mass movement of gases in and out of the lungs from the atmosphere to the arterial blood is referred to as external respiration Gas exchange and utilization at the tissue level is referred to as internal respiration. The latter is beyond the scope of this presentation.

Ventilation

The exchange of gases between the atmosphere and the alveoli occurs because of a pressure gradient existing between the atmosphere and the lungs Air flowing from the region of high pressure to one of low pressure allows for volumetric changes to take place With each breath the volume of gas inspired becomes humidified, warmed to body temperature and mixed in the dead space as it traverses the conducting nonrespiratory channels (nasal passages, pharynx, larynx, trachea, bronchi and bronchioles). The gas entering the lungs because of cyclic movements is well mixed but not absolutely uniformly distributed. This unequal distribution is due to stratification of the inspired gases, to regional variations in ventilation, and to sequential ventilation with some of the dead space air added to the alveolar air. The pulmonary volume can be conveniently divided into two compartments, the alveolar volume and the dead space volume. A subdivision of the total lung capacity showing volumes and lung compartments is presented in FIGURE 3. These will be discussed in detail in Chapter 36

Mechanics of Breathing

In the mass movement of air from the atmosphere to the alveoli and out again there are certain mechanical factors involved which cause resistance to ventilation, require energy and create work On inspiration, for example, air flows from the atmosphere to the alveoli Neuro-

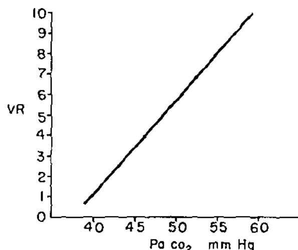


Fig 1 —(A) Ventilatory response to CO_2 stimulation Ventilation (VR) expressed in multiples of the resting ventilation

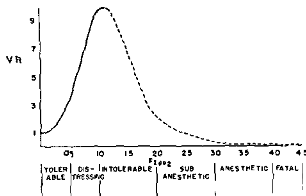


Fig 1 —(B) Relationship of pulmonary ventilation and the fraction of inspired CO_2 Ventilation (VR) in multiples of the resting ventilation Increase in ventilation occurs with concentration of CO_2 up to 10 per cent, beyond this depression and coma result (From Gray, J. S. Pulmonary Ventilation and Its Physiological Regulation. Springfield, Ill, Charles C Thomas, 1949)

muscles, especially the diaphragm. He states that tonus of the diaphragm is influenced by the inflation of the lungs and the reflex regulates the position of the diaphragm.

Peripheral and Proprioceptive Reflexes

The basic peripheral reflex was demonstrated in 1868 by Hering and Breuer, who observed that in the rabbit if the vagi are intact, changes in volume of the lungs influence respiration, inflation of the lung inhibiting inspiration and deflation exciting inspiration. With expansion of the lung, stretch receptors help initiate an inhibitory stimulus which is transmitted via the

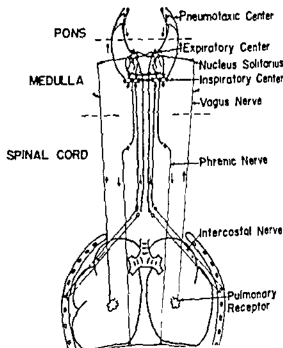


Fig. 2 —Neurogenic pathways involved in the regulation of pulmonary ventilation (From Fulton, J F Howell's Textbook of Physiology Philadelphia, W B Saunders Co , 1946)

vagus nerve, eventually terminating inspiration. On expiration a similar inhibitory stimulus eventually terminates expiration and allows inspiration to take place These reflexes are in part evoked from receptors in a reciprocal relationship and are said to be found in the bronchi and in the parenchyma of the lungs. Other special receptors have been postulated to be present in other parts of the body, in the pleura, the periphery of the lungs, air passages, joints and muscles, with appropriate nervous pathways to the cerebral centers playing a role in stress and disease states

Peripheral Chemoreceptors

One of the most outstanding discoveries in respiratory physiology occurred at the turn of the century when Heymans and co-workers demonstrated the presence of chemoreceptors in animals Actually, very little is known about these chemoreceptors and the role they play in breathing. It is generally accepted that in man the chemoreceptors in the aortic and carotid bodies are important in some way in the regulation of breathing. There is disagreement, however, as to the mechanisms involved. One

concept holds that the main control of ventilation lies in the medulla and the respiratory center and the chemoreceptors come into action as emergency mechanisms. Hypoxia may depress the center, making it unresponsive to the usual chemical stimuli, thereby allowing the chemoreceptors to dominate. Another concept suggests that there is normally a combined effect of direct stimulation of the center and a reflex stimulation by way of the chemoreceptors. The nervous supply to the chemoreceptors consists of a branch of the glossopharyngeal nerve of Hering and a depressor nerve which joins the vagus. Hypoxia is considered to be the primary stimulus for these peripheral chemoreceptors.

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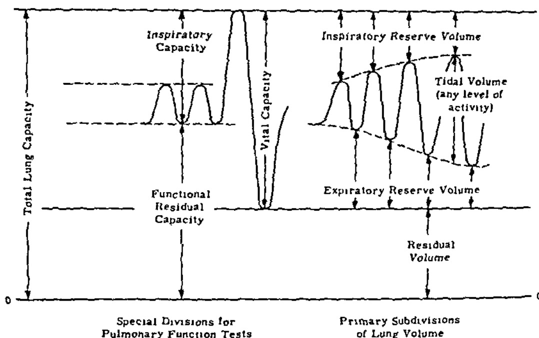


FIG 3 —Subdivision of the total lung capacity, showing volumes and lung compartments. (*From Fed Proc, vol 9, 1950*)

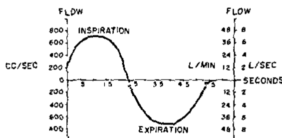


FIG. 4 —A schematic representation of a normal pneumotachogram showing the time-flow relationship Volume can be obtained by planimetry or integration after previous calibration

genic influences result in muscular contraction, an actuating force consisting of contraction of the muscles of the chest wall, rib elevation and the diaphragmatic descent resulting in an expansion of the alveolar gas, a lowering of the alveolar pressure and a flow of air into the lungs Normally, instantaneous flow rates of 30 to 50 L. per second can be obtained. (FIGURE 4 is a normal pneumotachogram showing the flow-time relationship of a respiratory cycle.) Resistive forces opposing this flow of air are: (1) the elastic tissue resistance, (2) nonelastic tissue resistance and (3) airway resistance. These factors exert their greatest influence on inspiration, which normally is an active process Expiration is passive, occurring as a result of recoil except with forced expiration.

The elastic structures on inspiration must be stretched by muscular effort. Removal of this effort results in a recoil. The greater the muscular effort, the greater will be the elastic stretch, and in relation to the lung the greater volume contained therein. Compliance is a term used to express this elasticity, which can be defined as a measure of the distensibility of the elastic components of the tissue. The slope of the line that results from plotting the external force against the increase in volume is a measure of the distensibility of the lungs and the thorax and expresses compliance, more specifically, it is the volume change per unit of pressure change acting across the lungs and thorax. The measurement of lung compliance alone is commonly made by simultaneous recordings of the transpulmonic pressure as reflected by the intrathoracic pressure and the lung volume measurement during a static state The pressure volume relationships as described by Fenn and coworkers represent the sum of the elastic power generated by both the lungs and the thorax and enables one to determine the pressure required to distend the lungs and the chest

A force is necessary to move nonelastic tissue such as the rib cage and the abdominal contents during inspiration The friction resulting in the tissue that moves is referred to as the

viscous resistance. This resistance depends upon the velocity of motion. The faster and deeper the breath, the greater the resistance developed. At the beginning of inspiration it is zero, it is maximum at maximal flow, and zero again at the end of inspiration

Airway resistance alone depends upon the number, the length, the cross section of the air passages and the rate and nature of air flow through them The smaller the tubes the greater the resistance, with less air flow occurring per unit of pressure. The larger the tubes the greater the air flow. Air flow through the tracheobronchial tree can be laminar, turbulent or a combination Ordinarily, it is laminar except at the larynx and at areas of branching of the tracheobronchial tree where eddy formations are created. The pressure required to produce laminar flow follows Poiseuille's Law, is related to the velocity, a constant.

$$P = \frac{8l\lambda V}{\pi r^4}$$

P = pressure
V = flow rate
λ = viscosity of flowing medium.
l = length of tube
r = radius

Laminar flow is dependent on the viscosity and independent of the density of gas. In turbulent flow the pressure produced is related to density and not to viscosity Since both laminar and turbulent flow are mixed in the tracheobronchial tree the total pressure is the sum of both. Two other factors must be considered in airway resistance These are (1) the cohesive force (surface tension) as might occur in atelectasis, and (2) the inertia of the system The latter is so small as to be considered insignificant. Disease states which cause constriction or blockage of the airways lead to an increased airway resistance, as, for example, in asthma, edema, emphysema and productive bronchitis.

In overcoming the resistive forces mentioned above, work is done by the muscles of respiration It has been estimated that the nonelastic tissue resistance accounts for 10 per cent of the work done, the air flow resistance 25 per cent and elastic tissue resistance 65 per cent of the total work of breathing. In the performance of work, energy and oxygen consumption are necessary. The ratio of the work done to the energy consumed represents the mechanical efficiency of the breathing apparatus. It has been stated that the useful work done represents only 8 per cent of the total energy consumed. Just as with other muscles of the body a greater contraction takes place than is necessary for the amount of work done normally. In disease states, however, this energy cost of breathing may play a very significant role in the ability of an individual to ventilate adequately. Mechanics of breathing, along with the technics for evaluation, are discussed in greater detail in Chapter 37.

Alveolar Ventilation

With a normal tidal volume of 500 cc. and a rate of 12 breaths per minute the total minute ventilation would be 6 L. It is not the minute ventilation, however, but the effective alveolar ventilation which is important. Since the dead space ventilation in the normal adult is about 150 cc the effective alveolar ventilation in our example would be 350 cc. per breath or 12 times 350, 4200 cc. per minute. The following equations are used to express alveolar ventilation.

$$V_E = \dot{V}_D + V_A$$

$$\dot{V}_A = f(V_T - V_D)$$

$\dot{V}_E$ = volume of gas expired per minute total ventilation.
$\dot{V}_D$ = dead space ventilation (per minute).
V = alveolar ventilation (per minute)
f = frequency of breathing
V_T = tidal volume.
V_D = dead space volume.

The region where ventilation but no gas exchange takes place is referred to as the dead space. Normally the anatomic dead space and the physiologic dead space are one and the same. This is not so in disease states, in which ventilation without blood perfusion can take place It is important to remember that the rate and tidal volume do not alone determine the effective alveolar ventilation

Alveolar air consists of a mixture of oxygen, nitrogen, carbon dioxide and water (TABLE 1)

TABLE 1—*Percentage Composition of Dry Air*

	N_2	O_2	CO_2
Inspired	79 02	20 94	0 04
Alveolar	80 40	14 00	5 60

TABLE 2—*Partial Pressures of Respiratory Gases* (Normal Resting Sea Level Values)

	P_{O_2} mm Hg	P_{CO_2} mm Hg	P_{N_2} mm Hg	P_{H_2O} mm Hg	Total mm Hg
Inspired air (Dry)	160	0 3	600		760
Alveolar air	103	40	570	47	760
Arterial blood	95	40	570	47	752
Mixed venous blood	40	47	570	47	704
Tissues	<30	>50	570	47	700

Air within the lungs is saturated with water vapor at all times regardless of the gases breathed Each of the gases in the mixture exerts a pressure directly proportional to its concentration. The sum of the partial pressures of the gases is equal to the atmospheric pressure of the gas mixture (TABLE 2)

$$P_B = P_{O_2} + P_{CO} + P_{N_2} + P_{H_2O}$$

P_B = barometric pressure
P_{O_2} = partial pressure of oxygen.
P_{CO_2} = partial pressure of carbon dioxide
P_{N_2} = partial pressure of nitrogen
P_{H_2O} = partial pressure of water

The partial pressure of any gas is dependent upon its relative concentration Dead space can be determined as follows

Bohr Dead Space Formula

$$V_D = V_E \times \frac{F_{ACO_2} - F_{ECO_2}}{F_{ACO_2} - F_{ICO_2}}$$

V_D = dead space volume
V_E = expired gas volume.
F_{ACO_2} = fractional concentration of *alveolar* CO_2
F_{ECO_2} = fractional concentration of *expired* CO_2.
F_{ICO_2} = fractional concentration of inspired CO_2.

The alveolar gas commonly measured represents a spatial and temporal mean. Venous blood entering the lungs equilibrates and leaves the lungs with values representing an average mixture of all of the alveoli perfused The composition of the alveolar air depends upon: (1) the inspired gas composition (TABLE 2), (2) the amount of carbon dioxide added from the blood, (3) the amount of oxygen removed from the alveoli, (4) the alveolar volume, and (5) the perfusion volume. The above-mentioned factors are interrelated A change in any one of them results in a change in all. Knowledge of the relationship *between these factors is important* before one can evaluate a given abnormality in respiratory function

The concentration of CO_2 in the alveoli is represented by the alveolar P_{CO_2} and is the result of elimination of CO_2 from the blood into the alveolar volume. The alveolar P_{CO_2} can be expressed as a ratio of the CO_2 elimination to the alveolar ventilation

$$\left(P_{ACO_2} \alpha \frac{\dot{V}_{ECO_2}}{\dot{V}_A}\right)$$

P_{ACO_2} = alveolar CO_2 tension
$\dot{V}_{ECO_2}$ = volume of CO_2 expired (per month)

Alterations in CO_2 elimination affect the alveolar P_{CO_2} unless the alveolar ventilation is also changed. Adjustments in alveolar ventilation take place normally to maintain a normal, constant alveolar P_{CO_2} of 40 mm Hg The functional residual capacity maintains the constancy of the alveolar P_{O_2} and P_{CO_2} throughout the entire respiratory cycle, both on inspiration and expiration

CO_2 elimination and oxygen uptake are expressions of the body metabolic activity. Normally, during alveolar blood-gas exchange, for every 10 molecules of oxygen taken up about 8 molecules of CO_2 are removed, resulting in a net decrease in lung volume, therefore, a larger *volume of air is inspired than is* expired This ratio of the CO_2 elimination to the oxygen uptake is commonly referred to as the respiratory quotient (RQ), or more recently as the respiratory exchange ratio (R). Changes in CO_2 elimination out of proportion to the oxygen uptake are reflected by a change in R Normally, about 40 cc. of O_2 is removed from every liter of air breathed. This can be expressed also as the

ventilatory equivalent or the number of liters of air breathed to remove 100 cc. of O_2 (normally 2.2).

$$R = \frac{(F_{ECO_2} \cdot \dot{V}_E) - (F_{ICO_2} \cdot \dot{V}_I)}{(F_{I\ _2} \cdot \dot{V}_I) - (F_{ECO_2}\ \dot{V}_E)}$$

Alterations in the respiratory exchange ratio invariably mean abnormal CO_2 elimination and are profoundly altered by the alveolar ventilation. Oxygen uptake, however, is not altered by change in alveolar ventilation alone.* Respiratory disturbances alter the respiratory exchange ratio initially. This is referred to as an "unsteady state." Regular adjustments take place to restore the respiratory exchange ratio to normal in the so-called "steady state." An increase in alveolar ventilation without an increase in oxygen uptake results in a fall in the alveolar P_{CO_2}, a state of hyperventilation. In exercise, the oxygen uptake increases, the P_{CO_2} remains constant, a state of hyperpnea and not hyperventilation exists. Hypoventilation, on the other hand, occurs whenever alveolar ventilation is inadequate, the alveolar P_{CO_2} increases, the pH drops, and the alveolar P_{O_2} decreases (Fig. 5).

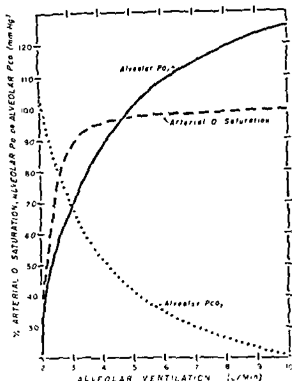


Fig. 5.—Relationship of O_2 saturation, alveolar P_{O_2}, alveolar P_{CO_2} to alveolar ventilation. (From Comroe et al. The Lung, Chicago, Yr Bk Pub., 1955.)

Ventilation-Perfusion Ratio

The interrelationship between alveolar ventilation and perfusion is a most important one in the determination of the alveolar composition. The ventilation-perfusion ratio relates the alveolar ventilation to the *cardiac output* and can be expressed as follows

$$\frac{\dot{V}_A}{\dot{Q}} = .8 \text{ (normal)}$$

$\dot{V}_A$ = alveolar ventilation
$\dot{Q}$ = cardiac output.

Alterations of this ratio affect the alveolar P_{CO_2} and the P_{O_2}. Changing the ratio does not alter body oxygen metabolism but it does alter the CO_2 elimination and hence the alveolar P_{CO_2}. The effect on the alveolar P_{CO_2} is the same whether the ratio is altered by a change in the alveolar ventilation, the cardiac output, or both. Increased body metabolism normally does not alter this ratio. With increased oxygen consumption, CO_2 output is increased and the alveolar ventilation increases to prevent hypercapnia, cardiac output increases and the ratio remains unchanged. If oxygen demand and utilization by the tissues remain constant, changes in the arterial P_{O_2} can occur because of altered ventilation perfusion ratios. If a given blood flow is associated with a decrease in alveolar ventilation, the alveolar P_{O_2} must fall, consistent with the removal of the same amount of oxygen from the smaller volume.

The alveolar equation is an expression of the ventilation perfusion–gas exchange relationship and enables one to calculate the alveolar oxygen.

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{CO_2}\left(F_{I_{O_2}} + \frac{1 - F_{I_{O_2}}}{R}\right)$$

$P_{A_{O_2}}$ = tension of alveolar O_2.
$P_{I_{O_2}}$ = tension of inspired O_2.
P_{CO_2} = tension of alveolar or arterial CO_2.
$F_{I_{O_2}}$ = fraction of inspired O_2.
R = Respiratory exchange ratio.

Distribution of blood and gas in the lungs, along with technics for evaluation, are discussed in greater detail in Chapter 38.

Alveolar–Capillary Blood Gas Exchange

In the passage of oxygen from the alveoli to the ultimate combination with hemoglobin, the following structures must be traversed (a) the alveolar wall, (b) interstitial space, (c) capillary endothelium, (d) plasma, and (e) red cell membrane. These structures are commonly considered as a unit and referred to as "the pulmonary membrane" Any change in one results in a change in the entire unit The diffusion of gas across the pulmonary membrane follows the well known laws of physical diffusion.

$$\frac{Q}{t} = D \times A \times \Delta P$$

Q = quantity of gas
t = time.
D = diffusion coefficient of the pulmonary membrane
A = diffusion area
ΔP = mean pressure gradient across the membrane.

The total surface area for diffusion (A) normally is very large, approximately 90 M^2 (50 × BSA) Since there is no direct way of measuring the surface area for diffusion, it can be included in the diffusion coefficient of the membrane in the following manner

$$\frac{Q_{O_2}}{t} = D_{O_2} \times \Delta P_{O_2}$$

$$D_{O_2} = \frac{Q_{O_2}/\text{unit time}}{\Delta P_{O_2}}$$

The D_{O_2} is defined as the amount of oxygen diffused per unit of time per unit of pressure gradient, normally 20 ml /min./Hg. This means that for each millimeter of mercury pressure difference across the alveolar capillary membrane, 20 cc. of oxygen will diffuse per minute. Since the resting D_{O_2} is only a reflection of the functioning surface area, it is not a measurement of the diffusing capacity of the lungs or the maximal D_{O_2}. This latter measurement, obtained during exercise and by stressing the gas exchange mechanism, is normally 60 cc. per minute per mm Hg. Other factors involved in the diffusion of gases are the capillary bed, the patency and proximity of the alveoli to the capillaries, and the physical characteristics of pulmonary system which leads to interalveolar or interstitial pulmonary edema, thickening of the alveolar or capillary membranes, destruction of alveoli, reduction in the capillary bed, or separation of alveoli from capillaries will affect the oxygen diffusing capacity of the lungs

Gaseous equilibrium is obtained along the course of the pulmonary capillaries. Diffusion is rapid at first and becomes slower as the alveolar air and blood approach equilibrium The length of the capillary and the rate of blood flow determine the extent to which equilibrium occurs Normally, blood is exposed in the capillaries to the alveoli for 0 7 second (FIG. 6). No gas exchange occurs in the peripheral arteries or to a significant degree, if at all, in the chambers of the heart. Evidence supports the contention that pulmonary capillary blood comes into equilibrium with the alveoli perfused with respect to the alveolar CO_2. Mixed venous P_{CO_2} enters with a mean P_{CO_2} of 47 mm. Hg, rapidly equilibrates with alveolar air and leaves with a P_{CO_2} of 40 mm Hg

For practical purposes, oxygen comes into equilibrium with the pulmonary capillary blood except for a very small fraction, 1 to 2 mm Actually, an O_2 gradient of 8 to 10 mm Hg exists between the alveolar P_{O_2} and the arterial P_{O_2} (A-a gradient) This gradient has two components. (1) the membrane, the alveolar capillary gradient, and (2) the venous admixture or the capillary arterial gradient The latter effect is due principally to bronchial and thebesian vein circulation as well as nonuniformity of alveolar ventilation.

No gradient exists for CO_2 between the alveoli and the arterial blood, at least, none that can be measured This is because of the small mixed venous and alveolar CO_2 difference (7 mm normal), and the rapid and highly diffusible gas, a steep CO_2 dissociation curve (FIG. 7) Alveolar-capillary diffusion technics and evaluation are discussed in Chapter 39.

TRANSPORTATION OF BLOOD GASES

Oxygen Transport

Oxygen is transported in the blood either physically dissolved in the plasma or in combination with hemoglobin. Normally the physi-

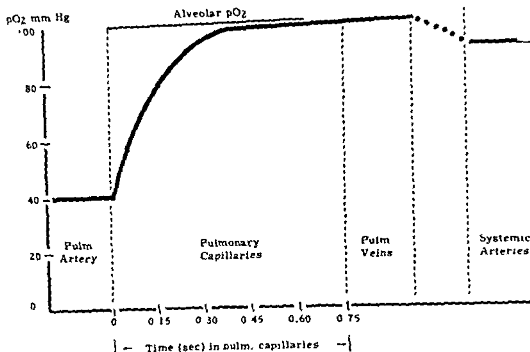


FIG 6.—Alveolar capillary diffusion. Mixed venous blood enters the pulmonary capillaries with a P_{O_2} of 40 mm Hg. The blood is exposed to the alveolus for not more than 0.7 second for equilibration of gases. The arterial P_{O_2} is slightly lower than that in the pulmonary capillary because of normal venous admixture. (From COMROE ET AL.: The Lung. Chicago, Yr. Bk. Pub., 1955.)

cally dissolved O_2 represents a very small portion of the total oxygen transported, 0.3 per cent, with room air breathing at an alveolar P_{O_2} of 100 mm Hg. However, with pure oxygen breathing this physically dissolved oxygen may be as high as 2 volumes per cent, assuming a P_{N_2} of zero. With a normal cardiac output this amount of oxygen is enough to take care of 40 per cent of the oxygen requirement. Most of the oxygen transported by the blood (99.7 per cent) is done so as oxyhemoglobin (HbO_2), each gram of hemoglobin being capable of binding 1.33 cc. of oxygen if completely saturated. The oxyhemoglobin content depends on the per cent saturation and the oxyhemoglobin capacity, the per cent saturation being a function of the P_{O_2}. The remarkable feature of the union of oxygen with hemoglobin is the readiness with which the gas is released from the combination when its tension in the surrounding medium is reduced. This is a very labile combination.



$$Hb + O_2 \rightleftharpoons HbO_2$$

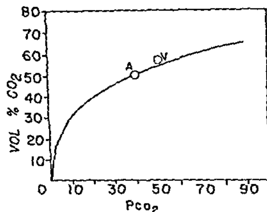


FIG 7.—CO_2 dissociation curve of human blood. A = arterial point, V = mixed venous point.

Hemoglobin from which oxygen has dissociated is called reduced hemoglobin. The relationship between the partial pressure of oxygen and the per cent saturation of hemoglobin with a gas, in other words, the proportion of the oxyhemoglobin to reduced hemoglobin, can be shown in the form of a curve, the oxyhemoglobin dissociation curve (FIG. 8A). This curve is obtained by mixing a sample of blood at body tempera-

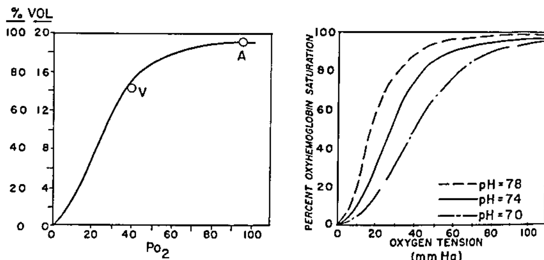


Fig 8 —(A) *Left* Normal human oxyhemoglobin dissociation curve at 38 C, pH 7 40 A, arterial point, V, mixed venous point (B) *Right* Effect of pH on the oxyhemoglobin dissociation curve of human blood

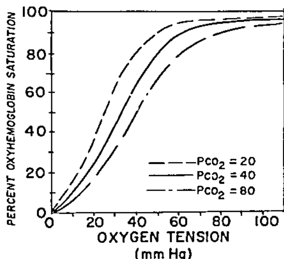


Fig 8 —(C) Effect of CO_2 change on the oxyhemoglobin dissociation curve of human blood

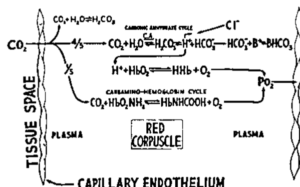


Fig. 9.—Transport of carbon dioxide in the blood CO_2 competes with O_2 for the hemoglobin molecule. A high P_{CO_2} speeds O_2 release at the tissue level, and a high P_{O_2} speeds CO_2 release at the alveolar level.

ture with known tensions of oxygen in a tonometer Equilibration takes place and then the proportion of oxyhemoglobin to reduced hemoglobin is determined and plotted on the chart, with the oxygen tensions along the abscissae and the per cent saturation along the ordinate. An S-shaped curve is obtained Important features of the oxyhemoglobin dissociation curve are. (1) A large drop in P_{O_2} can occur at the flat portion of the curve before significant changes in oxygen saturation exist (2) At the steep portions of the curve, small changes in P_{O_2} result in marked changes in oxygen saturation. This permits relatively large volumes of oxygen to be removed without much drop in the partial pressure of oxygen and allows for a rapid liberation of the gas at the lower partial pressure. (3) The curve is shifted to the right by a rise in P_{CO_2} or a decrease in pH Alkalosis, on the other hand, shifts the curve to the left (Figs 8B and 8C).

Carbon Dioxide Transport

Carbon dioxide is transported in the arterial blood as physically dissolved carbon dioxide, 5 per cent, as the HCO_3^- ion in chemical combination as a bicarbonate, 80 per cent, in direct combination with hemoglobin as carbaminohemoglobin, 15 per cent (Fig. 9) Physically dissolved CO_2 in the plasma is in equilibrium with the water vapor as follows:

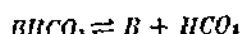


$$CO_2 + H_2O \rightleftharpoons H_2CO_3$$

This physically dissolved CO_2 is important in that it accounts for the diffusion pressure of

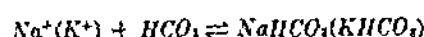
P_{CO_2} and is the major factor in the control of pulmonary ventilation.

The plasma HCO_3^- ion is the anion in the following equilibrium



$$BHCO_3 \rightleftharpoons B + HCO_3$$

The base is chiefly, sodium "fixed base." CO_2 diffuses rapidly from the plasma into the red blood cells An enzyme carbonic anhydrase present in the red blood cell accelerates the hydration and dehydration of CO_2. This ionic balance is maintained by the "chloride shift" The HCO_3^- ion combines with the cation, sodium and potassium.



$$Na^+(K^+) + HCO_3 \rightleftharpoons NaHCO_3(KHCO_3)$$

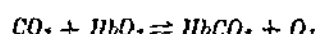
The H^+ ion released in the red blood cell combines with hemoglobin



$$H^+ + HbO_2 \rightleftharpoons HHb + O_2$$

This combination maintains an acid base balance and forces oxyhemoglobin dissociation in the systemic capillaries.

The carbamino hemoglobin, a direct combination of CO_2 with hemoglobin on the NH_2 radical, is an isohydric reaction



$$CO_2 + HbO_2 \rightleftharpoons HbCO_2 + O_2$$

Carbon dioxide competes with oxygen for the hemoglobin molecule A high P_{CO_2} speeds O_2 liberation at the tissue level and a high P_{O_2} speeds CO_2 release at the alveolar level Reduced blood has a higher CO_2 capacity than saturated blood. Reduced blood provides more cations, sodium and potassium to combine with CO_2 as $BHCO_3$ The higher pH and P_{O_2} of the arterial blood favor dissociation of carbamino-bound CO_2 The CO_2 capacity of the blood is the amount of CO_2 found at a P_{CO_2} of 40 mm. Hg and a pH of 7.40. The CO_2 content is the total amount of CO_2 present in the blood under existing conditions Carbon dioxide plays a major role in the acid-base balance as a part of the buffer system of the blood as shown by the ratio of the bicarbonate to the carbonic acid The Henderson-Hesselbalch equation.

$$pH = 6.1 + \log \frac{BHCO_3}{H_2CO_3}$$

The alveolar ventilation is an important factor in the determination of the P_{CO_2} and the blood pH. Disturbances in respiration will alter the Pa_{CO_2} and the H_2CO_3, leading to respiratory acidosis or alkalosis Any alterations of the Pa_{CO_2} are compensated for by changes in the H_2CO_3 to maintain a normal relationship.

Transport of Nitrogen

Nitrogen is transported entirely as a dissolved gas. The total amount of nitrogen in the blood and tissues is about 1.5 L., or 1 cc per 100 cc. of body fluid The partial pressure of nitrogen in the alveolar air, the arterial blood, the tissue fluid and the venous blood is approximately the same. Because there is no metabolic utilization of nitrogen, there is no effective respiratory exchange. However, the body fluid nitrogen declines whenever the alveolar nitrogen falls, as might occur during hyperventilation, on ascent to altitude, and on breathing pure oxygen. The speed of clearance of nitrogen from the lungs is an excellent test of distribution of gases within the lungs. Denitrogenation of the lungs and tissues is useful in preventing bends and in the treatment of subcutaneous emphysema.

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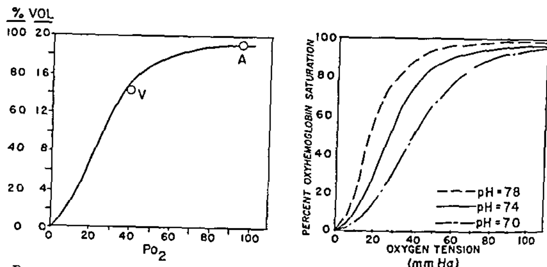


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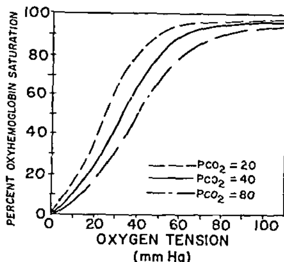


FIG 8 —(C) Effect of CO_2 change on the oxyhemoglobin dissociation curve of human blood

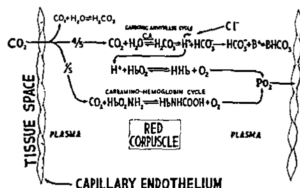


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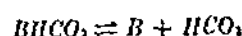


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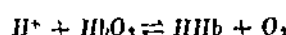
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Bronchial Drainage and the Phenomena of Cough

By HYLAN A. BICKERMAN, M.D

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THE primary function of the pulmonary system in respiration is the maintenance of normal tissue oxygen tensions and the elimination of carbon dioxide Adequate gaseous exchange is facilitated by the remarkable capacity of the lung complex for effective self cleansing or bronchoelimination The maintenance of this self-cleansing property is of vital importance to *an organ constantly exposed to an external environment* laden with noxious gases, irritating dusts, particulate matter and microorganisms The magnitude of this problem is brought into sharper focus when it is realized that the lungs normally ventilate between 600 to 1,000 cubic feet of air daily and that this air contains anywhere from 5 million to 100 million particles of suspended matter per cubic foot depending on the dustiness of the atmosphere. In addition, the inspired air must be altered to the proper temperature and humidity. The efficiency of *this "air-conditioning" system is reflected in* the preservation of the patency of the respiratory airway and its freedom from irritation or infection

When the elaborate protective mechanisms for bronchoelimination are impaired, bronchial drainage becomes inadequate, resulting in the accumulation and retention of secretions This favors the development of infection, provokes bronchospasm with ineffectual paroxysms of coughing and leads to obstructive dyspnea. The consequences of these pathophysiologic changes are inadequate alveolar ventilation with disturbances in gas exchange, patchy areas of atelectasis and pneumonitis, and irreversible damage to the bronchial wall or lung parenchyma itself. Death may ensue from any of these factors or from asphyxia due to widespread obstruction of bronchi and bronchioles by retained plugs of viscid secretion. Inadequate bronchial drainage is one of the principal defects encountered in the majority of all disease states affecting the bronchopulmonary system. The importance of this problem in clinical medicine is emphasized by a recent survey by Fox[19] who reported that respiratory disease accounted for 45 per cent of all illnesses seen in general practice.

The pathophysiologic factors concerned with bronchoelimination and measures designed to *facilitate adequate bronchial drainage* will be discussed under the following headings. (1) the ciliary mechanism including mucus formation, (2) phagocytosis and lymphatic drainage, (3) bronchial dynamics during normal ventilation, and (4) the phenomena of cough.

The Ciliary Mechanism

The epithelial lining of the conducting portion of the airway extending to the first portion of the respiratory bronchioles is of the ciliated columnar type, becoming cuboidal in the bronchioles *Mucin-secreting goblet cells* are interspersed between the ciliated cells The cilia are approximately 7 0 microns in length and 0 3 micron in diameter Bollinger[11] found an average of 8.5 cilia per cell There are no cilia present on the vocal cords or the anterior commissure of the larynx, hence, all secretions propelled by ciliary activity must traverse the posterior commissure in their passage toward the pharynx. The cilia are capable of sweeping particulate matter at rates of 0 25 cm. to 1 0 cm. per minute in the smaller bronchi and as rapidly as 3 to 4 cm. per minute in the trachea As much as 600 ml. of respiratory tract fluid per day is capable of being removed by the ciliary mechanism of the normal lung in man Although motility appears to be independent of neurogenic control or the effect of gravity, ciliary activity is peculiarly vulnerable to changes in the "mucus blanket" with which it forms a functional unit. Studies by Proetz[31] have demonstrated that the cilia become ineffective as a

protective mechanism when the secretion of mucus is too scanty or profuse, too dilute or concentrated. When the bronchi become filled with secretions, ciliary action fails and only a churning motion is imparted to the retained material by air movement during the respiratory cycle. Certain drugs such as morphine, local anesthetics and glycerine have been shown to retard ciliary motility. The effect of changes in pH is controversial. Negus[33] was unable to demonstrate any inhibition with citric acid and bicarbonate solutions in vivo in contrast to the findings of other investigators who employed isolated preparations.

The nature of the respiratory tract fluid is of considerable interest since it provides the necessary elements of the "mucus blanket." The alveoli and terminal bronchioles form a thick, scanty secretion which is diluted by the less viscid mucin secretions from the goblet cells and the acinar bronchial glands. These secretions are composed of 5 to 6 per cent solids, 50 per cent of which is mucin. Three types of sputum have been described by Basch, Holinger and Poncher[6] as a result of studies on patients with bronchiectasis. The first portion of sputum to be coughed up is a mucus plug which is highly viscous and not ordinarily affected by expectorant agents. The second type, constituting the major portion, is a liquefied fraction with low viscosity. Liquefaction of this portion results from the secretion of fluids from the bronchial glands, resorption of solid constituents and bacterial and enzymatic activity. Expectorants act mainly on this portion of the sputum, rendering it more fluid and less tenacious. The third type is scanty and viscid and is formed in the most dependent sections of the respiratory tract. These areas are not to be considered as having sharp zones of demarcation since considerable mixing occurs within the airway as a result of air movement.

The initial barrier to the penetration of particulate matter into the lower respiratory tract is provided by the hairs at the entrance to the nasal passages which serve as a gross filter. Smaller air-borne particles traversing the sinuous course of the respiratory airway come in contact with the "mucus blanket" covering the trachea and bronchi and become adherent. Alexander[1] has stated that the largest particle capable of penetrating to the alveoli is approximately 0.15 mm. in diameter. Since the vast majority are larger in size, they are trapped in the proximal portions of the airway. Nevertheless, it is clinically apparent that smaller particles do reach the alveolar portions of the lung. The factors concerned with such penetration are (1) the particle size, (2) the concentration of particles in the inhaled air, (3) their physical and chemical characteristics—whether in a solid or liquid phase, chemically inert or irritating, (4) the depth of respiration and (5) the duration of exposure. The importance of the time factor is indicated by the increase in the amount of carbon in the lung parenchyma as a function of age. Barclay,[5] using radiopaque substances, demonstrated striking differences between air-suspended and fluid-suspended particles. The solid material consisting of bismuth carbonate dust was largely confined to the trachea and bronchi, but the fluid droplets rapidly penetrated to the periphery of the lung. Droplets of oil were not impeded by the epiglottis and, depending on the viscosity of the liquid and the position of the body, tended to flow to the alveolar level. In spite of the large numbers of micro-organisms present in the inhaled air, the normal lung is usually sterile. In this connection, the question of whether bronchial secretions are bacteriocidal is controversial.

Since the ciliary mechanism is largely responsible for the removal of secretions under normal conditions, any deterioration in its activity places a greater burden upon other factors involved in bronchoelimination. In fact, Hilding[21] has stated that death from asphyxia may occur with failure of the ciliary system resulting in the accumulation of large amounts of secretion. Although the regenerative powers of the normal ciliated epithelium of the respiratory tract are considerable, irreversible change with transition to a stratified squamous type has been noted with chronic infection, low grade irritation, viral diseases such as influenza and vitamin A deficiency. Senescent atrophy has been described but the factor of aging per se is highly debatable. In long-standing bronchial asthma, many of the ciliated cells may be re-



FIG 1 —Microphotograph of sputum specimen from a patient with severe bronchial asthma, showing bronchial epithelium distended with mucus (From BICKERMAN, H A, SPROUL, E E, AND BARACH, A L Dis Chest 33 347, 1958)

placed by mucin-secreting goblet cells, resulting in an excessive production of mucus This is illustrated in the microphotograph of sputa from a patient with bronchial asthma prepared by Papanicolaou technic (FIG 1)

PHAGOCYTOSIS AND LYMPHATIC DRAINAGE

While the mechanism for removal of foreign material from the tracheobronchial airway is remarkably effective, extraneous matter which has penetrated beyond the respiratory bronchioles is disposed of less easily. The principal means of removal is by phagocytosis The type of cell participating in this process depends on the nature of the foreign substance For example, acute infections such as the pneumonias evoke a polymorphonuclear response. Chronic infection and the presence of irritant particles result in the appearance of lymphocytes and macrophages The latter, known as "dust cells," are of particular importance since they are present under normal conditions and are capable of being mobilized in large numbers in response to noxious stimuli Certain types of particles, such as carbon, may pass directly into the lymphatics without phagocytosis.

Following engulfment of the particle, destruction may take place through the action of intracellular enzymes, such as occurs with certain bacteria, or the phagocytes may migrate to the alveolar ducts and bronchioles and be eliminated via the air passages Others may pass into the lymphatic channels and be deposited in the peribronchial or perivascular nodes or be carried to the hilar lymph nodes. In pathologic states such as the pneumoconioses, obstruction to lymphatic drainage may result from the accumulation of swollen phagocytic cells In addition, irritating substances may be liberated in the interstitial tissue following degeneration of overladen macrophages. The net result is increased fibroblastic activity, culminating in a diffuse fibrosis Since the movements of the lung during respiration are extremly important in aiding lymph flow, the increased rigidity imposed by fibrosis interferes further with lymphatic drainage. Miller[27] noted that the amount of lymphoid tissue increased from childhood to old age and considered this largely due to the irritation arising from the constant inhalation of noxious substances Robertson[32] believed that the epithelial cells of the bronchi have little if any ability to phagocytose foreign material

BRONCHIAL DYNAMICS

The importance of the role played by air movement and bronchial dynamics during normal respiration in facilitating bronchial drainage is debatable Klassen and his co-workers[23] believe that only a minor part is played by respiratory movements, while ciliary activity is most important in clearing the smaller bronchi and bronchioles and the cough reflex most effective in the upper air passageways Nevertheless, the protective aspects of this mechanism are readily apparent clinically. The inhalation of irritating gases or vapors produces a marked narrowing of the bronchial tree by reflex action Most of this spasm, often manifested by a wheeze, occurs at the glottis and in the bronchioles devoid of cartilaginous support. Air

movement is abruptly halted in midinspiration by voluntary limitation of diaphragmatic motion. This reflex is mediated by sensory receptors in the nasopharynx and upper airway and is frequently accompanied by associated attempts at bronchoelimination such as sneezing or retching By itself, this mechanism is usually inadequate.

Anatomically, the smooth muscle of the respiratory tract extends from the trachea to bronchioles of 0 1 mm or less in diameter. Of importance is the arrangement of these muscle bundles in a lattice-work or geodesic pattern (Miller). Bronchoconstriction is produced by contraction of the muscle fibers, which may result from direct stimulation of the vagus nerve or its branches or reflexly through appropriate stimulation of afferent receptors in the overlying mucosa Conversely, the excitation of a sympathetic arc produces relaxation. The muscle bundles in the bronchioles appear to be five times as thick as those in the larger bronchi relative to the cross-sectional diameter of the lumen Functionally, the smooth muscle together with its elastic tissue framework is intimately concerned with the expansion and contraction of the lung during respiration.

In order to aerate the inexpansile portion of the lung behind and above the hilum during inspiration, the lung and hilum shift forward, outward and downward in a spiral manner. The tracheobronchial tree not only becomes elongated but luminal size increases as well On expiration, shortening occurs, associated with a narrowing of the air passages Macklin[25] has shown that these movements occur in all portions of the tracheobronchial tree, being relatively greater in the smaller bronchi. While a number of investigators employing x-ray, including high speed cinema-fluoroscopic technics and direct bronchoscopic observation, agree that a definite wave of motion travels from the [illegible] studies by Luisada[24] showed the existence of continuous action currents in the tracheobronchial musculature, and the evidence presented by Di *Rienzo*[18] strongly suggested an active peristaltoid or "milking" movement of the bronchi. Ellis,[13] however, favored the view that these changes were passive in character and secondary to variations in intrathoracic pressure associated with movements of the lung and thorax in normal respiration. Paralytic dilatation of the bronchi was not observed after vagotomy and there was no decrease in bronchial movements or the caliber of the bronchi following denervation. This will be discussed further in the section on the cough mechanism.

Whether active or passive, it has been suggested that these peristaltoid movements of the bronchial tree assist in the expulsion of foreign material and retained secretions. In certain pathologic states such as bronchiectasis, Santé[34] states that the severance of continuity of a diseased portion of the bronchus from normal adjacent areas results in the loss of normal bronchial movement with respiration. The inability to eliminate excessive secretions is attributed to this loss of motor function, with resultant "puddling" of purulent material and atelectasis of lung tissue supplied by the involved segment.

In addition to its importance in ventilation, the piston-like motion of the diaphragm is a valuable contributory aid in draining the lower lobes of the lungs With limitation of diaphragmatic motion, secretions tend to collect on the affected side, producing bronchial obstruction. The effect of diaphragmatic paralysis on the clearance of lipiodol from an otherwise normal lung has been studied by Klassen.[21] Pooling of contrast substance with delayed elimination was *uniformly observed*

Interference with air flow resulting in inadequate ventilation of peripheral lobules may seriously *interfere* with bronchial drainage of the affected region. The absence of air distal to a bronchus or bronchiole obstructed by a mucus plug or foreign body results in patchy areas of atelectasis During inspiration, there is an increase in negative pressure behind the obstruction and the cohesive forces present in the atelectatic area tend to diminish the effectiveness of cough and other protective measures. Day and his co-workers, in studies on rats, showed that the re-establishment of adequate ventilation following occlusion of the feeding

bronchus was much more difficult in the atelectatic lung as compared with a well aerated one In patients with intense bronchospasm or increased tonus, such as occur in bronchial asthma and pulmonary emphysema, further reduction in the lumina of the smaller air passages produces a marked reduction in air flow during expiration. Under certain circumstances, bronchial closure may occur, with absence of air movement This has been referred to by Dayman[15] as a "check-valve" mechanism and is of special importance in pathologic states associated with ineffectual cough Secretions which have accumulated within these collapsed bronchi are expelled with increased difficulty Measures designed to maintain the patency of the airway and improve air flow not only increase the efficiency of alveolar ventilation but facilitate bronchial drainage as well. In this regard, the benefit derived from appropriately applied positive pressure breathing and bronchodilator therapy has been extensively documented

The effect of posture on diaphragmatic motion and pulmonary ventilation has been reported by Wade and Gilson,[38] and Barach and Beck.[3] Their studies indicated that increased diaphragmatic excursion occurred in the head-down position This was particularly impressive in patients with pulmonary emphysema who exhibited little or no movement of the diaphragm while in the erect position. Fluoroscopy and spirographic tracings (Fig. 2) revealed a shift in the midposition when a head-down tilt of 15 degrees was assumed; the diaphragm was elevated from a low, flat, inspiratory position to a more normal, domed appearance. Restoration of diaphragmatic activity was accompanied by a decrease in the resting minute ventilation and a slight increase in the arterial oxygen saturation. Improved aeration of the bases and hilar regions of the lungs facilitated bronchial drainage. Furthermore, the benefit afforded by postural drainage in such conditions as bronchiectasis and lung abscess which takes advantage of the gravity displacement of secretions in the head-down position is universally accepted and hardly needs any further comment

The Phenomena of Cough

From the clinical standpoint, cough is probably the most prominent of the mechanisms involved in bronchial catharsis. It is defined as a sudden, forcible expulsion of air produced by active expiratory effort and is invariably accompanied by a sound of varying pitch and intensity As a protective, physiologic reflex, the primary function of cough is to clear the respiratory airway effectively by removing the offending irritant which stimulates the cough reflex. Since the lung is constantly exposed to an external environment containing countless numbers of irritant particles and vapors, the need to clear the tracheobronchial tree is an ever-present one Cough is universal in its distribution, occurring in health as well as dis-

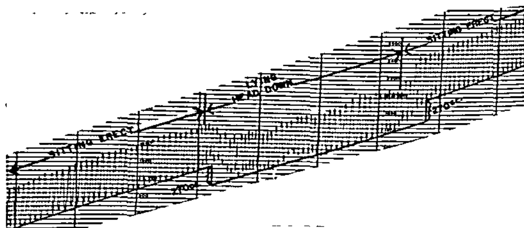


Fig 2.—Spirographic tracing of a patient with pulmonary emphysema, revealing a shift in the diaphragm to a more expiratory position when a head-down tilt of 15 degrees was assumed (From Beck, G J. *In* Barach, H and Bickerman, H. A., Eds. Pulmonary Emphysema Baltimore, Williams & Wilkins, 1956, chap 7 Reprinted by courtesy of the publisher.)

ease and not influenced by race, sex or age. While cough is frequently the presenting symptom in a wide variety of disease states ranging from a mild to a fatal illness, no correlation exists between the intensity of the cough and the gravity of the illness. Cough may be mild and hacking in bronchogenic carcinoma and harsh and paroxysmal in an acute tracheitis. Because of its universality, many individuals do not consider cough a serious enough symptom to seek medical advice. Furthermore, if present for a considerable time, a form of "adaptation" occurs and the patient becomes unaware of his chronic cough or pays scant heed to it, ascribing it to smoking, a dusty place of work, etc. On the other hand, the apprehensive individual may tend to exaggerate the intensity and severity of his cough.

Etiologic Considerations

Etiologic factors capable of evoking the cough reflex are so numerous that classifications based on the causative agent are unavoidably cumbersome. In general, cough most commonly arises from a stimulus within the respiratory tract, from the posterior pharynx to the terminal bronchiole. Other anatomic sites, including the pleura, diaphragm, and the external auditory canal, may give rise to cough with appropriate stimulation. While in the vast majority of cases, the causative agent responsible for cough is either an infectious or mechanical irritation within the lumen of the tracheobronchial tree; extrinsic compression of the airway may also provoke cough. TABLE 1 lists some of the more important etiologic factors.

TABLE 1.—*Classification of the Causes of Cough*

INFECTIOUS
Viral: common cold, atypical pneumonia, psittacosis, measles, influenza
Bacterial: the pneumonias, tuberculosis, pertussis
Mycotic: histoplasmosis, coccidioidomycosis, moniliasis, actinomycosis, blastomycosis
Spirochetal: syphilis, Vincent's infection
Rickettsial: typhus, Q fever
Parasitic: ascariosis, distomiasis
IRRITATIVE
Chemical: noxious gases and fumes, smoke
Mechanical: retained secretions, foreign bodies, improper use of voice
Thermal: exposure to marked variations in temperature
ALLERGIC
Asthma, vasomotor rhinitis
Loeffler's pneumonia, eosinophilic granuloma
NEOPLASTIC
Intraluminary: benign, malignant
Extraluminary with compression: lymphomas, Hodgkins, etc
VASCULAR
Heart failure with pulmonary congestion
Pericarditis
Pulmonary embolism, pulmonary infarction
Compression due to aneurysm
PNEUMOCONIOSIS
Silicosis, berylliosis, asbestosis, hemochromatosis
UNKNOWN ETIOLOGY
Collagen disorders: disseminated lupus erythematosus, periarteritis nodosa, scleroderma
Sarcoidosis
Pulmonary fibrosis, granulomatosis
PSYCHOGENIC
Habit spasm or "tic," tension states

With such a list of etiologic factors, although admittedly incomplete, it is no wonder that the investigation of the cause of cough may often be difficult. Certain facts elicited in the history and physical examination are *helpful in defining* the nature and origin of the cough. These include: (1) duration, (2) daily and seasonal variations in intensity, (3) dry or productive, (4) association with an acute respiratory infection and (5) quality of the sound and whether accompanied by changes in voice, wheezing or emesis. When productive, the character of the sputum on inspection and microscopic examination of a stained smear often provides *additional clues*.

In a recent survey of etiologic factors in chronic cough, Phillips and co-workers failed to show that residence in a generally more polluted urban atmosphere leads to an increased incidence of chronic cough. A positive correlation, however, was found between cigarette smoking and cough, and this was more striking in the older age group of smokers. While it is not the purpose of this section to review the clinical entities associated with cough, in my experience most, if not all, of the chronic "coughers" who smoke have associated chronic inflammatory changes in the mucosa of the

nasopharynx, larynx and trachea It is unwise, *even dangerous, to accept the view that a* cough is due to smoking without a thorough investigation designed to eliminate the possibility of underlying pathology.

Mechanics of Cough

Cough has been described as an explosive expulsion of air resulting in "the generation of a high linear velocity air stream with a high kinetic energy available for the acceleration and displacement of an object in the airway" (Ross, et al).[33] In considering the physical dynamics of cough, three chief phases have been described (1) inspiratory a sharp, deep inspiration ending with closure of the glottis; (2) compressive. contraction of the muscles of the thorax and abdomen with the diaphragm fixed, resulting in a high but momentary increase in intrathoracic pressure, and (3) expulsive· the rapid blast of air at high velocities when glottal opening occurs.

During the first stage, there is an increase in the vertical diameter of the chest The lower ribs are splinted by the internal intercostal and abdominal muscles, thus assuring adequate contraction and descent of the diaphragm during the inspiratory phase. This is accompanied by an elongation and widening of the entire tracheobronchial airway. On fluoroscopy, the *sternum is observed to move away from the* spinal column, thereby increasing the lateral width of the thorax. The cardiac silhouette and bifurcation of the trachea are also displaced anteriorly, while the angulation of the ribs assumes a more oblique course Franklin and Jonker[20] noted a two-fold increase in the cross-sectional diameter of the airway and likened the initial inspiratory phase to "the tensing of a strong bow." The inspiration preceding cough is usually deeper than normal, and Bucher[13] remarked that this was an integral part of the cough mechanism since a direct correlation appeared to exist between the depth of inspiration and the strength and effectiveness of the expulsive phase. Studies in cats revealed that blocking this initial increase in lung volume inhibited the expiratory gust of air when the cough reflex was artificially stimulated. Coryllos[14] noted that the expiratory blast of air was markedly reduced in the presence of unilateral paralysis of *the diaphragm which limited the* preceding inspiration In patients with respiratory paralysis due to poliomyelitis, clinical experience has demonstrated that with the aid of glosso-*pharyngeal breathing,* cough can be made more effective in eliminating retained secretions The enhancement of the cough mechanism by this maneuver is due, in part, to the greater volume *of air forced into the lungs and to an increase* in pulmonary compliance

Active contraction of the expiratory muscles, especially the abdominal (external and internal obliques, *the recti and the transverse* muscles of the abdomen), occurs during the short compressive stage, producing the "tussive squeeze." The diaphragm is maintained in a state of marked contraction so that the base of the thoracic cage becomes virtually a rigid structure. At the same time, the ribs and sternum are drawn downward, thus applying pressure to the entrapped air. The expiratory effort produced during this phase with the glottis closed produces a sharp increase in intrathoracic pressure, which has been recorded as high as 80 to 160 mm Hg.

With glottal opening during the *expulsive* phase, a blast of air is expelled from the respiratory passageway at a high initial velocity. Studies by Whittenberger and Mead[75] showed that *expiratory effort was greater for a brief* moment after the glottis opened than during the compressive phase. The rapid fall in intraluminal pressure while pressure within the surrounding parenchyma is still high results in a marked compression of the airway. The high velocity obtained is the result of (a) the intrathoracic to mouth pressure gradient, and (b) the contraction of the tracheobronchial lumina which reduces the cross-sectional diameters of the bronchial tree to between one-quarter to one-tenth of normal Since linear velocity varies inversely as the cross-sectional area, the velocity of escaping air has been *estimated* to be 0 5 to 2.0 M. per second in the bronchioles and between 50 to 120 M per second at the glottis. The initial velocity of air expelled during a vigorous cough has approximated the speed of sound, 730 miles per hour, under special circumstances. The striking reduction in the

lumina of the air passages is largely responsible for the high kinetic energy characteristic of cough and serves to differentiate it from a forced expiration in which equivalent flow rates may be achieved.

The importance of the diaphragm in the cough mechanism has been stressed by Banyai and Joannides.[2] As already mentioned, during the first phase it is responsible for approximately 40 per cent of the inspired air and during the second phase helps maintain the rigidity of the thoracic cage thus facilitating the development of high intrathoracic pressures. During the third stage, it relaxes simultaneously with the opening of the glottis and rises sharply. The extent of this rise appears to be related to the intensity and character of the cough. By grading the transmission of the increased intra-abdominal pressure to the lung, the diaphragm serves to regulate and adjust the expulsive efficiency of the cough. The excursion of the diaphragm during cough is three to four times greater than during normal ventilation. In ordinary coughing, it does not rise to its fullest height but seems to act as a controlling mechanism, determining the amount of abdominal pressure that is exerted upon the chest. When the cough response becomes paroxysmal in character due to severe irritation, a series of short, intense expulsive efforts with closure of the glottis between each occur, followed by a quick, deep inspiratory gasp and again a series of coughs. Under the fluoroscope, the diaphragm can be seen to rise sharply for a short distance with each expulsive effort as the volume of the thoracic cage diminishes.

Although considerable doubt has been raised concerning the ability of the cough reflex to drain secretions from the smaller bronchi, there is evidence that external compression of the entire airway produces a squeezing or "milking" action. Since the pressure gradient is lower in the trachea, luminal contents tend to be moved toward the mouth. While these changes may simulate a true peristalsis, Ross and his co-workers[22] have shown that the changes in bronchial diameters were synchronous with changes in intrapleural pressure and did not follow a sequential pattern as would be expected with a wavelike motion such as peristalsis.

In a series of interesting studies by Dayman,[15] the bronchi were observed, at times, to collapse during cough. Pneumotachographic tracings indicated that the intrathoracic airways were "check" valves on expiration. Although the bronchioles were normally supported against check valve closure by the elastic recoil of the pulmonary parenchyma, in certain pathologic states, such as pulmonary emphysema, air flow is markedly reduced or even momentarily interrupted. Collapse of the respiratory tract during cough in patients with pulmonary emphysema and bronchial asthma is suggested by low flow rates (leakage flow) despite intrathoracic pressures exceeding those found in healthy subjects.

Other factors which affect the mechanics of cough and modify its effectiveness in bronchoelimination are the presence of bronchospasm and the extent of alveolar aeration. In paroxysmal coughing provoked by severe irritation or bronchial obstruction, progressive narrowing of the bronchial lumina takes place, frequently accompanied by localized or diffuse bronchospasm. Secretions are trapped and cough is ineffectual in ridding the airway of retained material. Tussive insufficiency is often encountered in such bronchospastic states as pulmonary emphysema and severe asthma. Pneumotachographic studies by Bickerman and Itkin[10] indicated that the resistance to expiratory air flow in these patients during maximal cough was a prominent factor in the causation of tussive insufficiency. The striking improvement in the air flow dynamics of cough following relief of bronchospasm is illustrated in Figure 3. Barach and his co-workers[4] observed that the efficiency of cough was, in large measure, dependent on the aeration of alveoli previously poorly ventilated because of obstructing mucus plugs. When air can be made to enter behind the obstructive material, higher kinetic energy is developed during the expulsive stage and the plug is forced headward in a manner analogous to a bullet in a gun barrel. A remarkable feature of the cough response is the constancy of the cough pattern of each subject in terms of pressure-flow relationships. This is illustrated in

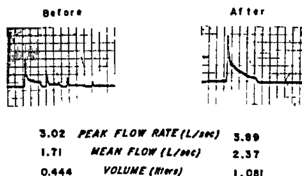


FIG. 3—Pneumotachographic tracings of the maximal cough of a patient with bronchial asthma, showing the striking increase in the peak and mean flow rates and the volume of air exhaled during the expulsive phase following relief of bronchospasm

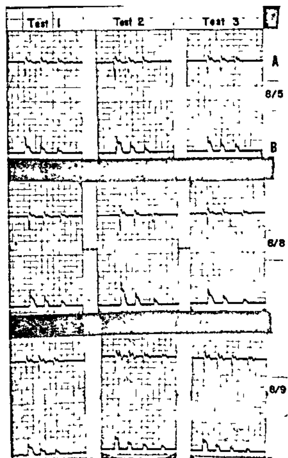


FIG 4—The constancy of the cough response is indicated by pneumotachographic tracings of cough produced by the inhalation of an irritant, citric acid The number of coughs and the pattern of air flow remain remarkably constant in the same subject on different test days. A, microphonographic tracing, B, pneumotachographic tracing

FIGURE 4, which shows pneumotachographic tracings of the cough response of a healthy subject exposed to citric acid aerosol on three separate occasions.

Regulation of Cough

Cough is a complicated reflex normally initiated by irritation of nerve endings within the epithelium of the respiratory tract It is partially under voluntary control, this control being more complete than that which exists with other comparable reflex mechanisms such as sneezing or vomiting In addition, there can be a considerable psychogenic factor in the genesis of cough as indicated by the so-called "nervous cough" and the wave of coughing precipitated by a few individual "barks" in a theatre

The stimuli capable of exciting the cough reflex fall into two broad categories: physical and chemical Since cough may result from irritation due to a wide variety of noxious stimuli, including mechanical, thermal, chemical, allergic and toxic agents, Bucher[13] has concluded that there are no specific cough receptors In- [illegible] receptors which appear to show considerable variation in their anatomic location within the respiratory tract The mucosa of the larynx and trachea, particularly the lower third including the carina, are most responsive to mechanical irritation, with only a weak response elicited below the level of the main bronchi. Mechanoreceptors may also be excited by abrupt volume changes in the tracheobronchial tree Studies by Widdicombe[37] indicate that sensitivity to chemical irritants such as sulphur dioxide is widely distributed throughout the respiratory passageway It would appear that the terminal bronchioles and alveoli contain few, if any, receptors since they are unresponsive to cough stimuli Tolerance often develops on continued stimulation, resulting in a decrease in excitability of the cough reflex or even complete refractoriness The chemoreceptors adapt somewhat slowly to the irritant, whereas the mechanoreceptors show rapid tolerance to continued stimulation

In addition to the tracheobronchial system,

afferent impulses which initiate the cough reflex may arise from many areas outside of the respiratory tract, including central stimuli which act directly on the "cough center." Normally, coughing is produced by the stimulation of the sensory endings of the glossopharyngeal and vagus nerves Both mechanically and chemically induced coughing are decreased by vagotomy, but combined vagotomy and sympathectomy are required to abolish the reflex. The major reflexogenous zones and their nerve pathways are illustrated in TABLE 2. Perhaps the most important cause of coughing outside of the respiratory system results from the stimulation of Arnold's nerve Inflammatory conditions about the meatus and in the external auditory canal, impacted cerumen, foreign bodies and even eczema may cause a chronic unproductive cough, particularly in children. Infrequently, dyspepsia or abdominal distention may provoke coughing by stimulating sensory fibers of the gastric branch of the vagus nerve.

There has been considerable speculation concerning the existence of a "cough center," and Bucher[13] has pointed out that most of the central mechanisms active in cough, such as facilitation of the preceding inspiration, closure of the glottis and active expiration, are not "cough specific " "Cough is only a special coordination of all these components and should be considered as part of normal respiratory regulation " It has become increasingly apparent that, like the respiratory center, the central mechanism for cough regulation is not nuclear in structure but is a part of the medullary reticular formation localized by Borison[12] in the dorsolateral region of the medulla at the level of the olivary bodies and adjacent to the rootlets of the vagus and glossopharyngeal nerves. Stimulation of this area at low frequencies produced alternate forceful inspiratory and expiratory movements simulating cough

The central nervous system pathways for cough have not been clearly elucidated. Various connections with higher centers are apparent in that considerable voluntary control and even suppression of cough is possible. Spread of excitation to the "vomiting center" is not uncommon in the paroxysmal coughing of pertussis as manifested by emesis, and, depending on the intensity of stimulation, cough may be accompanied by other sensations such as tickling, burning or pain. While the act of coughing interrupts the normal pattern of respiration, little is known of the inter-reactions between the central mechanism for cough and the respiratory center or other reflexes associated with respiration.

TABLE 2.—*Afferent Limb of Cough Reflex*

Receptor Area	Nerve Pathway
External meatus of ear	Auricular branch of vagus (Arnold's nerve)
Pharynx	Afferent fibers of glossopharyngeal and pharyngeal branch of vagus
Larynx	Superior laryngeal branch of vagus
Trachea Bronchi Pleura	Afferent fibers of pulmonary branches of the vagus
Diaphragm	Cardiac and esophageal branches of vagus
Pericardium	Afferent fibers of the phrenic nerve

From MODELL, W. Drugs of Choice. The choice of antitussive agents St Louis, C V. Mosby Co , 1958, chap 23 (Reprinted by courtesy of the publisher)

Pathophysiology of Cough

Although, physiologically, cough is a protective reflex designed to remove an offending irritant from the respiratory passages, there are numerous instances in clinical medicine when this reflex may be harmful There is some experimental evidence, for example, that the inspiratory rush of air accompanying the first phase of cough may actually spread infectious material to adjacent pulmonary segments. Lipiodiol has been observed to penetrate the finer ramifications of the bronchial tree during the act of coughing From a public health standpoint, the importance of cough as a primary factor in the airborne transmission of disease deserves considerable emphasis The high velocities attained during the expiratory phase converts liquid material within the airway into airborne droplets of various sizes, some with a diameter of 10 microns These droplet nuclei containing the infectious agent may be expelled

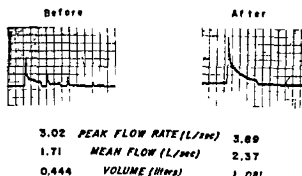


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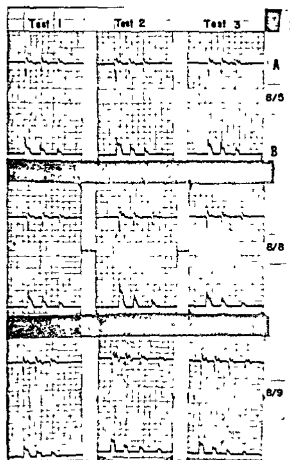


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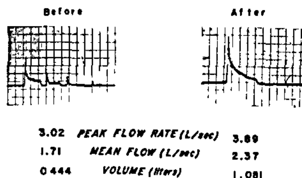


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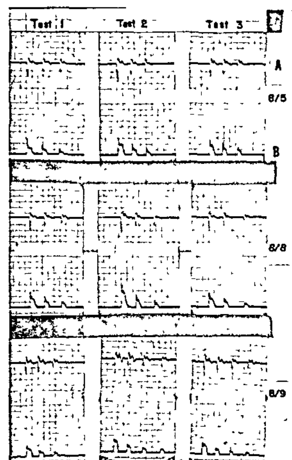


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FIGURE 4, which shows pneumotachographic tracings of the cough response of a healthy subject exposed to citric acid aerosol on three separate occasions.

Regulation of Cough

Cough is a complicated reflex normally initiated by irritation of nerve endings within the epithelium of the respiratory tract. It is partially under voluntary control, this control being more complete than that which exists with other comparable reflex mechanisms such as sneezing or vomiting. In addition, there can be a considerable psychogenic factor in the genesis of cough as indicated by the so-called "nervous cough" and the wave of coughing precipitated by a few individual "barks" in a theatre.

The stimuli capable of exciting the cough reflex fall into two broad categories: physical and chemical Since cough may result from irritation due to a wide variety of noxious stimuli, including mechanical, thermal, chemical, allergic and toxic agents, Bucher[11] has concluded that there are no specific cough receptors Investigations in animals and man, however, employing single unit recording, have demonstrated the presence of two distinct types of receptors which appear to show considerable variation in their anatomic location within the respiratory tract. The mucosa of the larynx and trachea, particularly the lower third including the carina, are most responsive to mechanical irritation, with only a weak response elicited below the level of the main bronchi Mechanoreceptors may also be excited by abrupt volume changes in the tracheobronchial tree Studies by Widdicombe[37] indicate that sensitivity to chemical irritants such as sulphur dioxide is widely distributed throughout the respiratory passageway It would appear that the terminal bronchioles and alveoli contain few, if any, receptors since they are unresponsive to cough stimuli. Tolerance often develops on continued stimulation, resulting in a decrease in excitability of the cough reflex or even complete refractoriness The chemoreceptors adapt somewhat slowly to the irritant, whereas the mechanoreceptors show rapid tolerance to continued stimulation

In addition to the tracheobronchial system,

coughing are urinary or stress incontinence, particularly in women, postoperative disruption of abdominal incisions, and spontaneous pneumothorax. Paroxysmal bouts of coughing in infants have been accompanied by periods of apnea, with a rapid fall in arterial oxygen saturation and marked bradycardia.

In conclusion, cough is a physiologic, protective reflex integrated into a complex system for maintaining the integrity of the respiratory apparatus by providing adequate bronchial drainage. There are instances when this reflex serves no useful purpose and its propagation may be harmful to the patient's well-being. But, even here, it may call attention to the presence of underlying pathology and provide an important clue in diagnostic assessment.

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for a distance of 15 to 20 feet following a cough and remain suspended in the atmosphere for long periods.

When the cough reflex is incapable of or ineffective in removing the provoking stimulus, tussive insufficiency results. In many suppurative diseases of the lung, cough is unable to remove the thick, tenacious mucopurulent secretions constantly being formed in response to the infection. The dry, hacking, irritative cough of some acute infections of the respiratory tract such as laryngitis, tracheobronchitis and pertussis may, in itself, become a major factor in retarding recovery by causing loss of sleep, inadequate food intake, nausea, and emesis. In obstructive disease of the tracheobronchial tree, such as tumors, foreign bodies, and chronic asthma and pulmonary emphysema, the cough reflex becomes self perpetuating and the resultant severe paroxysms of unproductive coughing cause serious debilitation of the chronically ill patient. When the cough reflex is mediated by an irritant stimulus outside of the respiratory airway, as in pleuritis, aneurysmal compression, or diaphragmatic pathology, no protective or useful purpose is served.

Banyai and others have stressed the harmful sequelae of tussive insufficiency. A few of the more important pathophysiologic consequences of chronic ineffectual cough will be presented in this section.

Pulmonary emphysema. Although many factors have been implicated in the causation of pulmonary emphysema, including chronic infection, protracted bronchospasm, alterations in blood supply and genetic "faults," a number of authors consider chronic cough as playing a principal role in the pathogenesis of this disease. There are, however, occasional cases of classical pulmonary emphysema in which absolutely no history of preexisting cough can be elicited. Bronchospasm is intensified by strenuous cough due to the mechanical irritation resulting from the stretching of the mucosal linings of the airway and the velocity of air movement itself. Furthermore, the "check valve" mechanism mentioned above acts like a ball-valve, permitting ingress of air but preventing its escape during the expulsive phase of cough. The resultant trapping of gas produces alveolar overdistention and, ultimately, rupture of alveolar septae with the formation of bullae and blebs. The deleterious effect of repetitively high intra-alveolar pressures on the elasticity or compliance of the lung parenchyma has also been implicated particularly in obstructive disease such as asthma and chronic bronchitis.

Stress fracture. Violent muscular contraction associated with severe paroxysmal cough may produce spontaneous fractures involving the ribs and occasionally the dorsal vertebrae. This has been termed stress fracture. Incidence figures vary from 0.5 to 2.0 per cent of all fractures in different series, with males affected twice as frequently as females. Osteoporosis was not a predisposing factor. The commonest sites for fracture were the sixth to tenth ribs in the axillary line, presumably due to the violent contraction of the abdominal external oblique muscles.

Cough syncope. This syndrome was first described by Charcot in 1876 and was thought to be a form of epilepsy. It is rare in women, occurring in 3 of 290 patients, but not uncommon in middle-aged males in the series reported by Sharpey-Schafer.[35] Unconsciousness may occur rapidly, within 3 to 5 seconds after the onset of a vigorous paroxysm of coughing. Measurements of intrathoracic and cerebrospinal fluid pressures during the height of the paroxysm have shown them to rise as high as 300 mm. Hg. A number of mechanisms have been implicated in the production of cerebral hypoxia and the resulting syncope. These include (1) decrease in venous filling pressure during cough with a fall in cardiac output and arterial blood pressure, (2) vagocortical reflex with marked peripheral vasodilation, and (3) pulmonary vasoconstriction with a fall in stroke volume. Recent studies by McIntosh, et al.[26] indicated that the "net pressure" within the cerebral vessels may approach zero for several seconds during a paroxysmal cough. The increased intracranial pressure transmitted from the spinal fluid pressure could mechanically squeeze blood from the cerebral vascular bed and collapse the vessels.

Other consequences of severe protracted

Pulmonary Physiology of the Newborn Infant in Health and Disease

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At birth, a physiologic adjustment of great importance concerns the change of the lungs from a nonfunctioning, fluid-filled state to a condition permitting the movement of an adequate amount of air in and out, with an effective diffusion to and from the blood. Since this transition must be made within a few brief minutes, it is not surprising that failure of some part of the respiratory apparatus is responsible for almost 50 per cent of all neonatal deaths. The most critical factors in the onset of respiration involve the control of respiration and the mechanical factors of lung expansion. The most frequent cause of respiratory failure is now known as "hyaline membrane disease." This and other features of respiration of the newborn infant will be discussed in the present chapter.

Fetal and Initial Respiration: Control

Gas exchange is effected in utero by the placenta, and the respiratory system of the fetus has no actual function until birth. It has long been thought, however, and more recently proved,[17] that the human fetus makes intermittent respiratory-like movements during intrauterine existence. The purpose, if any, of these movements is obscure, although they may reflect, in some manner, a "conditioning" of the respiratory muscles or the lungs themselves for later expansion, or a mechanism for removing respiratory tract secretions or debris. If amniotic fluid containing meconium (as in intrauterine hypoxia) passes into the lungs during these respiratory-like movements and obstruction and inflammation of the air passages result, this leads to the condition of "fetal aspiration syndrome."[22]

For information concerning the control of intrauterine respiratory-like movements, it is necessary to review the studies in animals by Barcroft and his co-workers.[5] Relatively early in intrauterine existence the fetus is capable of rhythmic movements of the thorax, but near term, these activities tend to be inhibited. Barcroft has suggested that sensory stimuli (tactile and thermal) are usually adequate to initiate respiration in the normal newborn infant, while chemical stimuli (increased P_{CO_2} and decreased P_{O_2}) provide emergency mechanisms when the respiratory center is depressed (Fig. 1).

The nature of both the birth process and the neonatal respiratory adjustment makes it obvious that some degree of hypoxia and hypercapnia must frequently occur. The fetus fortunately has a unique ability to withstand hypoxia,[20] and, in fact, by adult standards is hypoxic (arterial saturation = 50 per cent) continuously during the latter part of intrauterine life.[8] However, the mechanisms protecting the fetus from the phenomenon Barcroft has described as "Mt. Everest in utero" have not yet been well defined.

From the time of conception the fetus is exposed to a relatively low P_{CO_2}, since the production of progesterone causes the mother to hyperventilate. Within a few hours to a few days after birth the normal infant is able to adjust the blood gases to the normal levels found in adults.

Onset of Respiration: Mechanical Factors

Sufficient expansion of the lungs in the newborn infant requires adequate transpulmonary pressure produced either normally by the infant's own thoracic cage or artifically by some resuscitative technique (positive pressure to the upper airway or negative pressure around the thorax). This transpulmonary pressure must be large enough to overcome: (a) surface tension

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reduces the forces of surface tension opposing further expansions. This residual air is partly due to air-trapping, though it is primarily the result of a balance between the respective tendencies of the chest to expand and the lungs to collapse. Whether or not the chest, even prior to a respiratory movement, tends to expand at the moment of delivery from the birth canal has not been established. It is known, however, that there is apparently no measurable negative intrapleural pressure until the occurrence of respiration.[2]

Although transpulmonary pressure affects the inflation or deflation of the lungs per se, it should be recalled that in the newborn infant requiring artificial resuscitation, both the lungs and the thoracic structure must be expanded. The exact magnitude of these pressures is difficult to define as the thoracic compliance of newborn infants is not presently known, but apparently most of the force is required to expand the lungs themselves, and the thorax is relatively compliant.

In considering adjustments of the newborn infant's lungs, it is sometimes forgotten that there are also associated, important vascular adjustments often occurring simultaneously. For example, prior to birth and respiration, less than 20 per cent of the output of the right ventricle passes through the lungs, posing in itself an important problem in adjustment. At least one cause of this is the high resistance of the pulmonary blood vessels.[1] As soon as the first respiration has occurred, vascular resistance decreases and pulmonary blood flow increases, until within a few hours to a few days the entire output of the right heart passes through the lungs. Recently, Jaykka[25] suggested that this increase in pulmonary blood flow produced "capillary erection," which in turn contributed significantly to expansion of the lungs. The hypothesis was based on experiments conducted in vitro, using pulmonary vascular pressures sufficient to produce edematous rather than gaseous expansion of alveoli. More critical in vitro studies by Avery, Frank, and Gribetz[4] have indicated that pulmonary capillary erection probably contributes only a small fraction of the force necessary to expand the lungs of the newborn infant.

Sustained Respiration in the Newborn Infant

Control

Control of respiration in the newborn infant has recently been the subject of considerable study. Cross[16] has shown that increases in both inspired oxygen and carbon dioxide tensions stimulate respiration in the newborn, while decreased oxygen concentrations tend to produce respiratory depression. Furthermore, the respiratory response is modified by the gestational[16] and the postnatal age respectively.[30] For example, the least mature infant displays the poorest response to hypoxia. Cross suggests that "among the many factors which may be responsible for this 'immaturity,' the inability of the respiratory center of the infant to withstand oxygen lack plays a major part."

Another manifestation of immaturity of the respiratory center is the frequent occurrence of periodicity (Fig. 3) in the respiratory rhythm. The exact basis for this type of respiration, which is particularly common among premature infants, is unknown, but it is readily abolished by the addition of oxygen to the inspired air.[22] This suggests that hypoxic respiratory center

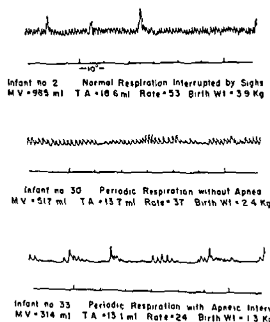


Fig. 3.—Tracings illustrating types of respiration in normal newborn infants.

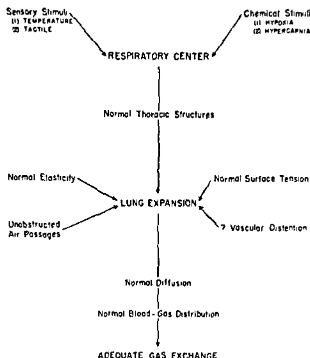


FIG 1 —Schematic representation of the onset of respiration (Reprinted, by permission, from, *Resuscitation of the Newborn Infant*, published by the American Academy of Pediatrics)

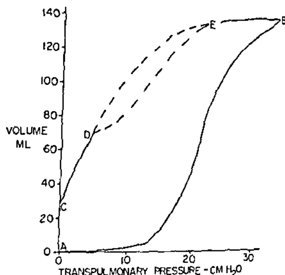


FIG 2 —(A) Typical pressure-volume curve of expansion of a gas-free lung A–B represents the initial expansion In the example, approximately 13 cm. H_2O pressure are necessary to overcome surface tension forces C represents deflation to O pressure with gas-trapping, and D–E represents subsequent inflations and deflations

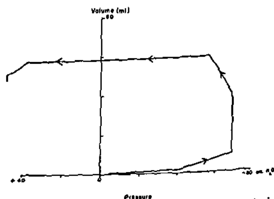


FIG 2 —(B) Pressure-volume relationships during initial respiration of a newborn infant weighing 4 3 Kg Here, 60–70 cm H_2O pressure were necessary to overcome the surface tension forces (From data of P Karlberg Second Conference on Physiology of Prematurity Reprinted by permission of the Josiah Macy, Jr , Foundation)

forces, (b) the elastic recoil of the lung and (c) tissue and air-flow resistance. Studies on expansion of gas-free, excised lungs of experimental animals[33] as well as the clinical investigation of newborn infants by Karlberg[27] indicate that the major factor opposing expansion of the lung is surface tension (FIG. 2A AND 2B). A lung that is made gas-free or the lung of a stillborn infant[23] can be expanded with relatively low pressures when the surface forces are minimized by using fluid as the expanding medium However, when gas is used, initial opening pressures for preparations in vitro must be much larger. In the living infant, opening transpulmonary pressures vary from 15 to as high as 70 cm. H_2O,[27] and this pressure for the most part is apparently expended to overcome surface forces

It is known that surface forces (P) are related to surface tension (T) and the radius (r) of a sphere, as shown in the following equation: $P \propto (2T/r)$. This offers at least one explanation for the more frequent failure of lung expansion encountered in premature infants (with their smaller air spaces) than in full-term infants. Furthermore, it has been shown recently by Avery and Mead[3] that actual surface tension itself may be unusually high in the premature as well as in infants with hyaline membrane disease This has led to the suggestion that physicochemical immaturity may interfere with the proper mechanical functioning of the lungs of certain newborn infants.

Once the initial surface tension forces have been overcome in the infant, the lungs do not again completely collapse (FIG 2A). The air remaining in the lungs at end-expiration greatly

ues in terms of basal metabolism* (1,610 calories per 24 hr. for the adult and 115 calories per 24 hr. for the infant), it is found that minute volume, alveolar ventilation, tidal volume and physiologic dead space are similar in the two groups. Functional residual capacity in the adult appears larger proportionately, whether basal metabolism or lung weight is used as the basis of comparison. Thus, in the adult FRC = 3.7 ml./Gm. lung, while in the infant FRC = 1.4 ml./Gm. lung tissue. This difference may be related to difficulties in obtaining true dry lung weights in the newborn infant; thus, most values presumably include considerable amniotic fluid. In any case, the effective ventilation of each breath bears the same relation to functional residual capacity in the infant and the adult.

Diffusion

Using the carbon monoxide steady-state method of Filley, studies of gas diffusion in normal newborn infants have been undertaken by Stahlman.[16] The data indicate that the carbon monoxide uptake for infants and adults is similar when compared on the basis of alveolar ventilation and oxygen uptake. The results will be interesting if the technic can also be applied to newborn infants with various forms of respiratory distress and degrees of lung expansion.

Abnormal Ventilation in the Newborn Infant

Causes of neonatal respiratory failure are classified in Table II. There is, of course, considerable overlap between the two major subdivisions. (a) central nervous system causes, and (b) lung abnormalities per se, but central nervous system depression is certainly the usual cause of failure to initiate respiration at the time of birth. Fortunately, with good anesthetic and obstetrical practice only occasional infants should now require initial resuscitation. On the other hand unfortunately, there has been only limited progress in reducing "fetal wastage" due to pulmonary failure, currently in the United States the most important single cause of death in the first year of life.[10] Although pul-

Table 2—*Principal Types of Respiratory Failure in Newborn Infants*

Central Nervous System Failure (Apnea Hypopnea)	Peripheral Respiratory Difficulty
Narcosis	Respiratory distress (congestive pulmonary failure, hyaline membrane syndrome, resorption atelectasis)
Prenatal or paranatal anoxia	Aspiration of meconium-containing amniotic fluid
Intracranial hemorrhage or trauma	Pneumonia
Central nervous system anomalies and others	Congenital anomalies and others

monary distress may be secondary to infection, congenital abnormalities, aspiration of foreign material (meconium), and to immaturity of the lungs, the commonest type of difficulty is associated with the formation of hyaline membranes in the alveolar ducts.

Hyaline Membrane Disease

Clinical Aspects

The terms "congestive pulmonary failure" and "resorption atelectasis" have been used to describe a syndrome now most commonly designated as hyaline membrane disease. Characteristically, this condition is seen in premature infants, *those born following intrauterine distress* and of mothers with diabetes mellitus;* however, the disease is seen occasionally in infants born without other complications at term. There is sometimes the suggestion that it occurs more frequently following delivery by cesarian section, but this has not been supported in a series of uncomplicated, elective sections. At the time the condition was originally described, the onset of symptoms was thought to occur during the first hours following delivery. However, with more careful observation, it has become apparent that the signs of respiratory difficulty in most, if not all, cases actually are present within a few moments of birth. Initially, there may be only tachypnea and/or minimal retrac-

* Basal metabolic rate was used as the basis of comparison because of uncertainties involved in the estimation of surface area, particularly in infants.

* Hyaline membranes also may occasionally occur in the lungs of older persons with such conditions as *uremic pneumonia, rheumatic fever* and various types of poisoning with toxic inhalants.

depression reduces the sensitivity of the regulating mechanisms.

Mechanical Factors

After the initial breath, ventilation of the lungs of newborn infants requires that essentially the same forces as encountered in adults be overcome, i.e , the elastic recoil* of the lung and the tissue and air-flow resistance These are, of course, modified by age and size For example, compliance gradually increases during the first few minutes and hours of life,[27] presumably the result of a gradual increase in the number of ventilated lung units In addition, compliance is directly proportional to the volume of the lung [14] Thus, compliance in the infant is low by adult standards (5 ml /cm H_2O) but relatively consistent with the adult when considered on a volume basis (069 ml cm H_2O/ml FRC for the infant and .051 ml /cm. H_2O/ml FRC for the adult) Actual and absolute pressures exerted to overcome the elastic recoil of the lung during quiet breathing are approximately the same (3 to 5 cm H_2O) in both infants and adults.

Although existing reports on newborn infants do not permit a critical separation of tissue and air-flow resistance, it is apparent that air-flow resistance is increased in infants due to their small air-passages. Actually the measurements of total lung resistance indicate the value as 29 cm H_2OL/ per second compared to 2 cm. H_2O/L. per second ie the adult This difference, in part, may be secondary since measurements of resistance in infants have been made during nose-breathing, while in adults the measurements are obtained with mouth-breathing technics Actual absolute resistive pressures during quiet respiration are of the same magnitude in infants as in adults, since peak flow rates for normal newborn infants during quiet respiration average 61 ml. per second (range 44 to 111 ml per second)[14]; for adults under comparable conditions peak flow rates are approximately 600 ml per second

The data on the mechanics of respiration together with measurements of minute and alveolar ventilation have made it possible to estimate the pulmonary work accomplished during respiration of the newborn infant. This is calculated as approximately 1,400 Gm. cm , apparently representing the same proportion of total body metabolism as in the adult.

Lung Volumes

The lung volume subdivisions of the newborn infant are shown in FIGURE 4. Although the value of residual volume is only an estimation and vital capacity is the maximum inspiration or expiration during crying, it is not unlikely that the subdivisions represent approximately the same proportion of the total lung volume as with the adult Other comparisons between respiration of the newborn infant and the adult are shown in TABLE 1 In comparing these val-

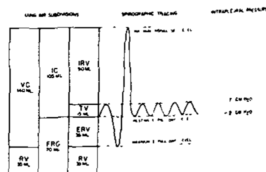


FIG 4 —Lung subdivisions of a newborn infant Vital capacity is crying maximum excursion The intrapleural pressure change has been determined but the absolute values are estimates (Reprinted from New England J Med *254* 562, 1956)

TABLE 1 —*Comparison of Adult and Infant Respiratory Data*

	70 Kg Adult	2 5 Kg Infant
BMR (cal /24 hr)	1,610	115
V_{O_2} (ml)*	232	17
V_{CO_2} (ml)*	200	12 3
V (ml)	6,000	498
f	12	31
V_T (ml)	500	15
V_A (ml)	4,140	355
V_D (ml)	155	5
V_D/V_T	0 31	0 32
V_{O_2}/V_A	0 067	0 062
V_{FRC} (ml)	2,700	70
$(V_T - V_D)/V_{FRC}$	0 13	0 13

* These volumes are STPD, all others, BTPS

* As shown in the studies of Clements and coworkers[12] and Radford,[31] the elasticity of the lung is intimately related to surface tension properties of lung extracts Thus, surface tension forces are important components of the elastic recoil

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* Basal metabolic rate was used as the basis of comparison because of uncertainties involved in the estimation of surface area, particularly in infants

* [illegible]
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of p[illegible] toxic inhalants.



FIG 5.—Infant with *proven* hyaline membrane disease showing marked sternal *retraction* (Reprinted, by permission, from the *New York State J Med* 58 372, 1958)

tion but the condition usually progresses, with striking sternal and intercostal retraction (FIG 5) and marked respiratory distress with cyanosis At this stage there may be evidence *of a* respiratory *and* metabolic acidosis In severe *cases, death* occurs between 24 to 48 hours of *age and* almost always by 72 hours *If* the infant survives for three days, the chances for spontaneous resolution of the process with no residual lung damage are excellent. The *mortality rate depends on* the criteria for diagnosis When all *cases* of idiopathic peripheral respiratory distress in the newborn are included in this general category the mortality rate is between 15 and 30 per cent.

From the description of the disease it is apparent that the diagnosis can be made only by history, a physical examination and by excluding other causes of peripheral respiratory distress such as pneumonia, aspiration of meconium-containing amniotic fluid, and congenital anomalies. Roentgenograms of the chest[22] are of considerable value in confirming the diagnosis, as shown in FIGURE 6. However, *the disease may* be present without the typical x-ray findings, and pneumonia may occasionally mimic the roentgen changes of hyaline membrane disease.

In summary, the diagnosis of hyaline membrane disease may be suspected in the living infant, apparently with considerable accuracy, but can only be confirmed at autopsy.

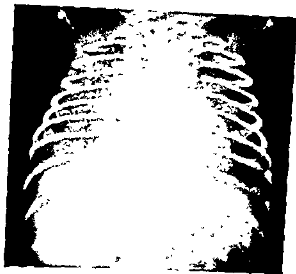


FIG. 6.—Chest x-ray of an infant with *proven* hyaline membrane disease, showing *reticulogranular* appearance throughout the lung fields

Pathologic Findings

At autopsy, the lungs are normal in size but with the color and consistency of liver and a specific gravity greater than 1 0 Microscopic examination (FIG 7) reveals striking atelectasis, with only a few large air passages apparently containing air. Usually, there is considerable evidence of capillary congestion. In the typical case, hematoxylin and eosin sections show obstruction of many of the alveolar ducts, with the characteristic pink, hyaline-like membranes[15] which apparently prevent inflation of the peripheral lung units and hence contribute to respiratory failure However, interpretation



FIG 7.—Photomicrograph (low power) of lungs of infant with hyaline membrane disease, showing marked atelectasis.

of such findings is confounded by the fact that the pathologic process itself has a wide spectrum; some of the clinically typical cases show large amounts of atelectasis but very few membranes Thus, the exact role of the membranes in the pathophysiology of the disease is not always explained Another particularly interesting feature of the pathology of the hyaline membranes is the timing: no membranes are found in infants dying within one hour of birth It is apparent, therefore, that respiration is necessary for the production of the membranes; presumably, some sort of precipitation and/or concentration of the membrane material is necessary.

Physiologic Findings

From the physiologic point of view, one of the most important abnormalities in the lungs of infants with hyaline membrane disease is the striking decrease of lung compliance. The obstruction of air passages by the membranes clearly reduces the volume of the functional lung[7] This, together with possible overdistention of remaining lung units, undoubtedly is largely the basis for the altered compliance The change in surface tension described by Avery and Mead[3] provides a still further and perhaps more basic explanation for the compliance decrease.

Whatever the basic causes of the reduction in compliance in infants with respiratory distress, the secondary effects lead to many changes in respiratory function (Fig 8). The functional residual capacity is reduced, presumably as a result of greater elastic recoil of the lungs The sternal and intercostal retraction is certainly the result of the large intrathoracic negative pressures necessary to move even a normal tidal volume. The terminal stages of the disease frequently are complicated by exhaustion of the respiratory muscles, an exhaustion which may be the result of the greatly increased work of respiration

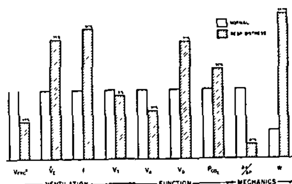


Fig. 8—Summary of physiologic findings in neonatal respiratory distress The open columns represent the normal infants and the cross hatched, the abnormal infants V_{FRC}, physiologic residual volume (data from Karlberg); V_E, minute volume, f, rate; V_T, tidal volume; V_A, alveolar ventilation; V_D, physiologic dead space; P_{CO_2}, partial pressure of CO_2 in the blood, $\Delta V/\Delta P$, lung compliance or elasticity; and W, work (Reprinted, by permission, from Respiratory Problems in the Premature Infant, Fifteenth M & R Pediatric Research Conference, 1955)

Another finding is the increase in minute volume[26] which apparently represents a compensatory adjustment to the increased physiologic dead space That this adjustment is incomplete is indicated by the cyanosis so frequently present and the occurrence of elevated blood P_{CO_2}.

Physicochemical Findings

Thus far, the discussion of hyaline membrane disease has centered around descriptive findings Is there additional information concerning the basic nature of the process? In 1956, Gitlin and Craig,[19] using an immunochemical technique, demonstrated that the membranes themselves were largely composed of fibrin Since amniotic fluid contains little fibrin or fibrinogen, they suggested that the membrane was probably the result of a transudate of plasma from the infant's own circulation into the air spaces Thromboplastin is present in amniotic fluid in sufficient quantities to change fibrinogen to fibrin, so in this manner the basic material for the membranes might be produced. A possible mechanism whereby plasma could be exuded more easily into alveoli but less readily absorbed has been suggested by Hughes, May and Widdicombe[24] in their report on edema in perfused lungs· "Once alveolar exudate is present the low transmural colloid osmotic pressure difference will hinder the re-absorption of fluid, for if the vascular pressures are restored to normal values, the capillary-alveolar barrier will again be impermeable to protein, and there will

be little pressure drop tending to the absorption of water."

As mentioned above, the studies of Avery and Mead[3] comparing the surface tension of extracts from the lungs of normal infants, those born prematurely and others with hyaline membranes suggest that an increase in surface tension may be an important factor in the failure of certain lungs to expand adequately at the time of birth. This may represent a physicochemical "immaturity" or a change secondary to some other, presently unknown chemical abnormality. In any case, it emphasizes, in general, the need for further research into the basic chemistry and physiology of normal and abnormal lungs, and, more specifically, calls attention to the importance of surface tension factors in expansion of the lungs of the newborn.

Another finding of interest is that of a reduced amount of profibrinolytic substance in the lung tissues of infants dying of hyaline membrane disease.[27] It has been suggested that a deficiency in fibrinolytic activity may contribute to the formation of hyaline membranes or may be the cause for failure of these membranes to be resolved. Certainly, such an enzyme deficiency, if confirmed by further studies, may contribute to the pathologic process and may, if a primary finding, serve as another example of chemical "immaturity" affecting the clinical status of an infant.

Animal Studies

One of the difficulties encountered in the clinical investigation of hyaline membrane disease is that it apparently does not occur naturally in any species other than man. A number of workers have produced hyaline membranes experimentally in animals but the entire picture of atelectasis, pulmonary congestion, and hyaline membranes has rarely been present.[6, 8, 9] All of the methods of production of hyaline membranes have either introduced plasma or amniotic fluid into the air passages or caused pulmonary damage and/or congestion, with secondary transudation of fluid from the animal's circulation into the alveoli. None of the methods has successfully stimulated the atelectasis which is so characteristically present in the naturally occurring disease. Moreover, none of these methods has suggested any counterpart in nature unless there is some sort of pulmonary congestion in the affected newborns on the basis of a hemodynamic abnormality during the period of perinatal adjustments which in part imitates the pulmonary congestion seen as a result of toxic inhalants. A possible example of this might be a delay in closure of the ductus arteriosus and increased pulmonary vascular pressures.

The importance and possible role of surface tension factors was pointed out by Pattle[31] on the basis of animal studies. "The finding that the lung lining substance appears only late in the fetal life of the guinea pig suggests that absence of the lining substance may sometimes be one of the difficulties with which a premature baby has to contend; such a defect may possibly play a part in causing some cases of atelectasis neonatorum. The appearance of a hyaline membrane might possibly be due either to a defective lining layer causing transudation from the blood or to excessive secretion of lining substance." These observations add weight to the studies of Avery and Mead on the lungs of infants.

Theories of Pathogenesis

Many theories concerning the pathogenesis of hyaline membrane disease have been proposed. Those centering around aspiration of gastric contents of amniotic fluid currently appear untenable. It has been suggested that oxygen toxicity may be important in naturally occurring hyaline membrane disease, as it is in the experimentally produced membranes. However, the fact that some respiratory abnormality is often present very shortly after birth suggests that O_2 toxicity does not play a primary role.

In view of the probably correct identification of the membrane material as fibrin, it would appear that a transudation of plasma from the infant's circulatory system into the air passages before or during the perinatal period is a cardinal feature of the process. The underlying cause of this transudation is certainly not presently understood but may result from a number of factors, such as pulmonary congestion on a hemodynamic or cardiovascular basis[23] or surface

tension changes leading to abnormal pressures across pulmonary membranes. A contributing factor might be a reduction in fibrinolysin, which, if present, would retard lysis of membranes once formed. As suggested by the work of Usher,[37] electrolyte abnormalities, whether secondary or primary, may contribute to cardiac insufficiency and secondarily to pulmonary congestion.

There are other theories but at the present time it can only be said that all hypotheses require further investigation and substantiation in animal and human work. Much is currently being learned in the clinical, physiologic and biological fields, and it is not too much to expect that a complete explanation of the pathophysiology of this condition will be forthcoming within the next few years. It is possible, undoubtedly, that multiple factors contribute to the production of hyaline membrane disease.

Therapy

The fact that hyaline membrane disease is self-limiting if the infant can be aided during the first three to four days arouses great interest in the possibility of useful therapy. Unfortunately, the nature of the basic pathophysiology of hyaline membrane disease is so poorly understood that a rational approach to treatment is not yet possible. Symptomatic treatment with supplemental oxygen is certainly indicated, and often useful when cyanosis is present, irrespective of any possible secondary risk of retrolental fibroplasia, obviously, the survival of the infant is the first consideration. Once this becomes probable, oxygen should be reduced and attention directed to the secondary conditions. It should be emphasized that oxygen concentrations over 60 to 70 per cent may in themselves cause pulmonary congestion and hence should be used with caution. The work of Silverman[34, 35] and his co-workers has shown that mists, with or without detergents, are not useful.

Symptomatic relief may also be possible with resuscitative devices such as that developed by Donald[15] and Goddard.[21] These at best, however, are of limited value in preventing or treating hyaline membrane disease. Other techniques for increasing lung expansion (such as continuous positive pressure) require further evaluation.

Is there more specific treatment? Can the membranes be dissolved? Craig, Fenton, and Gitlin[13] have shown that long exposure to high concentrations of a fibrinolytic agent (plasmin) will dissolve the membranes in vitro, but this substance, given either by aerosol or parenterally, remains to be evaluated in the infant with respiratory distress. If the studies showing a deficiency in fibrinolytic activity in the affected infants are confirmed, there is, at least, a rational basis for the administration of a fibrinolytic agent. Other enzymes such as trypsin have been tried in aerosols, but without success.

It has been suggested that heart failure may contribute to the pulmonary congestion, which in turn may lead to membrane formation.[29] So far, digitalis has been of little value. Carrington, Reardon and Shuman[11] have suggested treatment with glucose and saline or sodium bicarbonate solutions and apparently have had encouraging results. If this proves to be effective in the hands of others, the explanation may be in the correction of some sort of electrolyte imbalance, or in the supply of calories and fluid.

If surface tension changes are a fundamental part of the process in hyaline membrane disease, can the surface forces be reduced in any practical way? Filling the lungs with fluid is not practical and there is no specific nontoxic substance which will decrease surface tension when the lungs are inflated with air.

That a number of new technics are being tried is the most encouraging facet in the treatment of hyaline membrane disease. Certainly, many carefully controlled clinical trials are necessary before effective methods can be recommended for clinical application. In the meantime, it is essential that physicians concerned with the care of newborn infants remain critical so that technics of doubtful value are not emphasized

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The Ventilatory Response to Physical Effort

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The Ventilatory Equivalent

THE precision of the ventilatory response to the altered metabolic requirement is one of the most striking features of muscular exercise Over a relatively wide range covering almost all ordinary activities, the ventilation remains directly proportional to the oxygen uptake, so that the ventilatory equivalent for oxygen (i.e , liters of ventilation per 100 cc oxygen consumed) remains approximately 2 2 to 2 5. In average healthy subjects during severe work when the oxygen uptake approaches 2.0 liters per minute, there is a definite increase in the ventilation equivalent. The degree of effort and the effectiveness of oxygen uptake in relation to the ventilatory equivalent varies markedly in healthy subjects, in part, according to age and training This has been noted at much lower work levels in the presence of a variety of disease states [3, 10, 30]

The relationship of ventilation to oxygen consumption is displayed in FIGURE 1 In FIGURE 2 the ventilation (respiratory minute volume) is shown as a function of the oxygen consumption for a number of patients with rheumatic heart disease, hypertension, and various hyperkinetic disorders. That there tends to be a disproportionate increase in ventilation for a given work level in disease, as reported by many authors, is readily apparent There also is some evidence that the degree of ventilatory disturbance bears a quantitative relationship to the degree of cardiac or respiratory disability, thus increasing the clinical interest in such measurements.

Rate and Depth of Respiration During Exercise

An important characteristic of the normal response to effort is an increase in both the *tidal volume* (depth of respiration) and the *respiratory rate* (number of breaths per minute). The tidal volume increases steadily from 0.4-0.7 L to (approximately) 2-3.5 L and then plateaus, while the rate increases more slowly to meet the necessary ventilatory requirement This dual mechanism is in contrast to the response of the ventilation to other situations which are characterized by an increase in rate only, such as hyperthermia, atelectasis, protracted severe anoxemia, and various reflex stimuli. One of the important results of the increased depth lies in the fact that it reduces the effects of the anatomic dead space, resulting in elevated alveolar P_{O_2} even though the composition of the inspired air remains constant. As an approximation, the formula is alveolar ventilation = frequency × (tidal volume—dead space). Since the tidal volume increases significantly while the anatomic dead space remains relatively constant, total alveolar ventilation per breath is increased, with a resulting increase

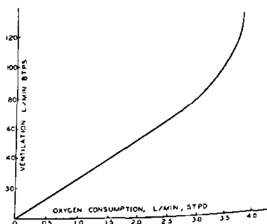


FIG 1 —The curvilinear relationship between ventilation and oxygen consumption in young normal subjects (taken from data published by F. S Grodins[17]) Of particular interest is the marked increase in the ventilatory equivalent beginning at an oxygen consumption of approximately 2 5 L per minute This change will occur at much lower levels in older normal individuals and in patients with cardiac or pulmonary diseases

in alveolar pO_2. Also, since the rate of alveolar capillary flow may be increased tremendously during exercise, the resulting increase in the gradient between alveolar P_{O_2} and the P_{O_2} of the mixed venous blood becomes of importance. Appreciation of this aspect of normal response to exercise is also important for evaluating experimental results in studies that attempt to demonstrate the presence of stimuli leading to the hyperpnea of exercise.

The time course of the respiratory minute volume during exercise with recovery is an important feature to consider in the evaluation of hypotheses pertaining to the control mechanisms regulating the hyperpnea of exercise and for appreciating the variations in the response of different subjects to exercise. During the initial phase—1 to 2 minutes of a constant exercise with abrupt (square wave) onset and cessation—the ventilation increases rapidly to attain a value approaching the maximum to be achieved if the exercise level is consistent with the de-

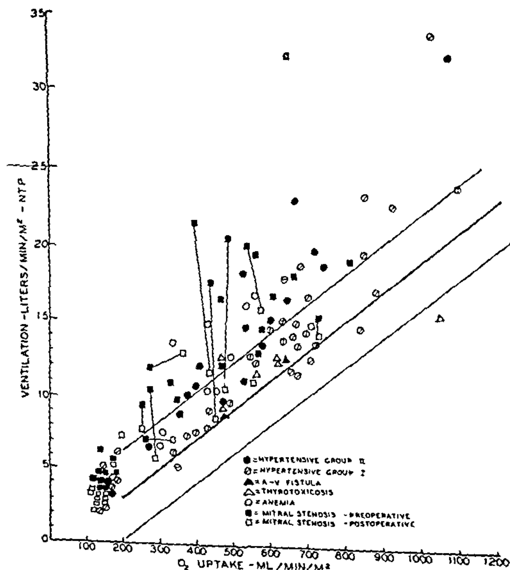


FIG 2 – ...

... of shortness of breath on exertion, while the Group I patients are those without any symptoms on ordinary activity

velopment of a steady-state (one that can be sustained for a protracted period). However, it may be important to emphasize that the ventilation slowly increases for a period of at least five to six minutes during a constant light exercise, unlike the oxygen uptake which usually reaches its maximal value during the first two minutes of such exercise Indeed, it may increase steadily for 10 to 12 minutes during near maximal "steady-state" exercise [21] During the recovery period the ventilation falls rapidly after a type of exercise that is easily tolerated, but it does not usually return completely to the pre-exercise level for at least five minutes. Following severe exercise (relative to the tolerance of the subject), both the level and duration of the post-exercise hyperpnea are increased. These observations strongly suggest a similarity of the hyperpnea of exercise and the time course of oxygen debt A quantitative relationship is further revealed by the greater ventilation noted during a given type of exercise for less fit subjects and for those with disorders of the cardiovascular or respiratory system Such a relationship is also consistent with the curvilinear relationship between ventilation and oxygen consumption shown in FIGURE 1 It is well known that the relationship between the oxygen debt and the oxygen consumption is similarly curvilinear.

In FIGURE 3, the oxygen consumptions and ventilations are plotted minute by minute, along with the instantaneous oxygen debt* for normal subjects and patients with mitral stenosis, at various levels of light-to-moderate work on a bicycle ergometer. Each of the plotted points represent the mean taken from the careful studies of four subjects by Donald and his colleagues,[3, 8-10, 30] all of the observations were made in a single laboratory, under almost identical conditions. A striking parallelism is noted between the time courses of the ventilation and the oxygen debt in each of the groups Since the ordinate scales are the same for all groups, a strong quantitative relationship becomes apparent The quantitative aspects of this relationship are presented in FIGURE 4, which plots the appropriate respiratory minute volume against the existing oxygen debt during each minute of rest, exercise and recovery.

Several points of interest should be mentioned First, there is a quantitative relationship of a high degree of familiarity, but with an apparent hysteresis effect. The greatest lag of ventilation is seen during the first minute of exercise, increasing with the severity of the exercise. Second, there is a lesser lag in the patients with mitral stenosis than in normal subjects, an interesting but unexplained phenomenon previously noted by Donald.[3, 10, 30] Third, during the last minute of exercise and throughout recovery the trends in all subjects, including those with mitral stenosis, fall along the same curved line In other words, the increased ventilation of the subjects with mitral stenosis is associated with a proportionate increase in the oxygen debt This relationship enhances the possibility that the excessive ventilatory response to exercise characteristic of a variety of cardiac disorders is a quantitative reflection, however mediated, of the disturbance of oxygen availability to the metabolizing tissues as equated to the oxygen debt

The parallelism between the unknown ventilatory stimulus of exercise and the metabolic rate has been pointed out and utilized in multiple factor regression analyses to predict ventilatory responses to effort. However, as may be seen in FIGURE 3, the time course of the total metabolic rate, the equivalent to the oxygen requirement for work, bears much less resemblance to the time course of the ventilation than does the instantaneous O_2 debt. The type of exercise employed by Donald was such that

* The instantaneous oxygen debt was calculated by summing the excess minute oxygen uptakes of the recovery period (i e , the increment over the resting values) and adding this to the sum of the minute uptakes during exercise This figure, divided by the minutes of exercise, yields the oxygen "requirement" of exercise [12] The difference between the measured oxygen uptake and the oxygen requirement is the increment of oxygen debt for that minute The sum of the increments to the end of any minute is the *instantaneous oxygen debt* at that time [24] During recovery,

These dynamic aspects of the oxygen lag have been recently emphasized and explored by Huckabee [12]

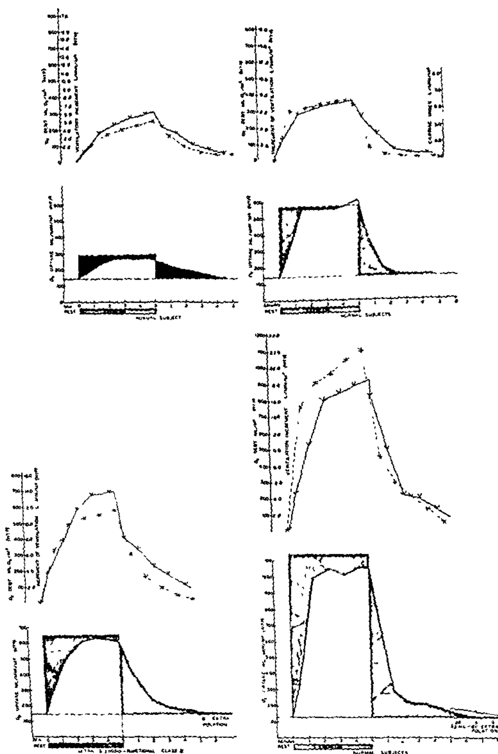


FIG 3.—The time courses of the ventilation (-v-), of the oxygen uptake (-•-), and the instantaneous oxygen debt (-x-) are shown. The oxygen "deficit" during exercise and the oxygen "debt" during recovery are indicated by the shaded areas representing the difference between the oxygen requirement and the oxygen uptake. To be noted is the similarity of the time course of the ventilation and that of the oxygen debt. (Constructed from tabular data of Donald et al [8, 39])

the time-course of the rate of work was very nearly a "square wave," as indicated by the oxygen requirement in the figures in contrast to the ventilatory curve. Although the time-course of the oxygen consumption is superficially similar to that of the ventilation, it is considerably less than the oxygen debt, *even at the* lowest level of work. Furthermore, it may be appreciated that at levels of work having an oxygen requirement greater than the maximal

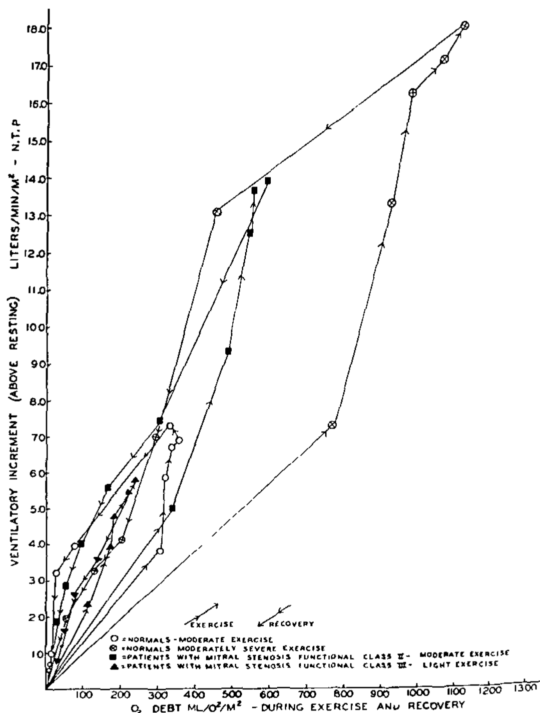


FIG 4.—The relationship between the instantaneous oxygen debt and ventilation during exercise and recovery (Constructed from tabular data of Donald et al [8, 10]) The measurements are plotted at one minute intervals There is an apparent "hysteresis" effect during exercise in the normal subjects, which is less evident in the patients with mitral stenosis. Normal and abnormal subjects appear to have identical relationships during recovery.

possible uptake of oxygen, both the oxygen debt and the ventilation would continue to mount precipitously after the oxygen uptake had reached its plateau, emphasizing the dissimilarity between the oxygen uptake and the ventilation.

Although the considerations mentioned above suggest a relationship between the ventilatory stimulus of exercise and some aspect of anaerobic metabolism, it must be pointed out that the observed points cover only a small segment of the possible range of the hyperpnea of exercise, the range of which may approach 70 L. per minute per square meter of body surface area. Current studies are in progress to test the extent and reliability of the correlation between the respiratory minute volume and the oxygen debt; but, regardless of the outcome of these studies, the importance of considering the time-course of the ventilation during exercise and recovery is apparent, both as to research and clinical applications.

The Regulation of the Ventilation During Exercise

Despite a succession of plausible, ingenious and often brilliant hypotheses based upon conjecture, indirect evidence and certain direct experimental data, neither the major stimuli nor the pathways of transmission to the respiratory center have been critically established. The most popular (historically) of the theories may be considered briefly.

Humoral

P_{O_2}. Perhaps the first of the integrated hypotheses as to the regulation of respiration was the suggestion that the respiratory center proportionately responded to the assumed decrease in the oxygen content of the arterial blood during exercise. This possibility was advanced by Rosenthal in 1882.[29] Many objections were immediately raised. Shortly after the theory was proposed, an increased oxygen content in the arterial blood of animals was noted during exercise and, in separate experiments, the "alkalinity" of the blood was shown to decrease with muscular contraction, suggesting an increase in the oxygen pressure as well.[13] Moreover, Haldane and Priestly found essentially no increase in ventilation until the oxygen percentage in the inspired air fell to about 13 per cent and alveolar oxygen to about 8 per cent.[18] In addition, they found that oxygen levels sufficiently low to produce cyanosis, dizziness, and headache were accompanied by a ventilation of only two to two and a half times that of rest, an observation amply confirmed since that time. More recently, the role of the oxygen tension during exercise has been re-examined as part of a multiple factor theory which proposes that the response is proportional to the algebraic sum of several factors acting together and that a small drop in oxygen tension could play a significant role.[3] The most direct data available at the moment on the actual changes in P_{O_2} are conflicting. Several investigators, using the microbubble technique of equilibration of arterial blood against known oxygen tensions, have reported a small but definite decrease in P_{O_2} during exercise.[11, 25] In another recent study, in which the oxygen tension of arterial blood drawn during exercise was measured polarographically, no decrease was found during severe exercise. In fact, a small increase was suggested.[27] Many studies have confirmed the fact that in normal subjects the oxygen capacity of arterial blood frequently increases, due to an increase in hematocrit, and that the saturation may decrease slightly or remain constant at low levels of exercise.[6] At higher levels of exercise there is a definite trend of the oxygen saturation to decrease very slightly. However, since both the increased capacity and the pH changes during severe exercise tend to increase the oxygen tension for a given degree of saturation, the results of the polarographic study seem most credible. At any rate, it would appear most unlikely that the very minor changes, if any, in the arterial oxygen tension are directly responsible for any real part of the hyperpnea of effort.

One of the reasons for the renewed interest in the arterial P_{O_2} is the fact that the hyperventilation of severe exercise may be remarkably and abruptly reduced by the addition of increments of oxygen into the inspired air. This phenomenon has been repeatedly observed, despite a simultaneous and definite increase in arterial P_{CO_2}.[21] This decrease in the

ventilatory equivalent has been accompanied by a proportionate decrease in lactate concentration, though the decrease is presumably not due to this factor since the change in lactate concentration lags behind the decrease in ventilation.[3] Since an increase in the ventilatory equivalent for oxygen has been demonstrated when the exercise was carried out with the subject breathing air containing a decreased oxygen pressure, it seems probable that such changes reflect the altered tissue oxygenation. These changes are apparently consistent with the relationship between the oxygen debt and ventilation, already discussed, although many alternative explanations have been offered. More direct experimental evidence is obviously desirable.

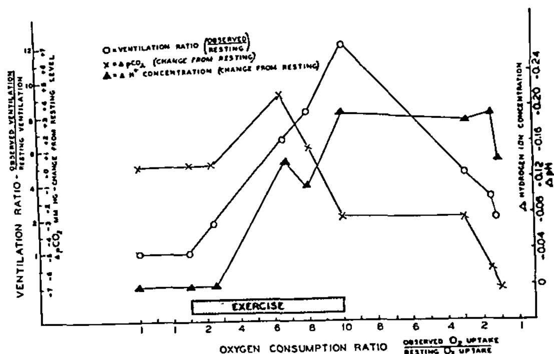
The arterial P_{CO_2}. Miescher,[26] in 1885, postulated that the CO_2 tension in the respiratory center is the factor which normally determines the lung ventilation. Twenty years later, Haldane, following a series of brilliant experiments,[15] reported that: (a) the ventilation varies directly as very small changes in alveolar CO_2 content, (b) the changes in ventilation are accomplished similarly in exercise, as regards depth and rate of breathing; (c) the increase in ventilation is achieved without unpleasant symptoms, and (d) the alveolar, and presumably therefore the arterial, pCO_2 is increased during exercise, though not quite in proportion to the increase in ventilation during severe exercise. This latter phenomenon was ascribed by Haldane to a greater increase in the CO_2 pressure in the respiratory center as a result of the decreased CO_2 carrying capacity of the blood presumed to follow the increased hydrogen ion concentration in strenuous exercise. "Even, however, if the CO_2 pressure was somewhat lower in the arterial blood during work in these experiments, the CO_2 pressure in the respiratory center may well have been higher. In consequence of the diminished alkalinity of the blood, its CO_2 carrying capacity was diminished. Consequently, with the same flow of blood through the center the CO_2 pressure in this blood would rise more rapidly than during rest, so that the CO_2 pressure in the center itself would rise just as it would do if the blood flow were diminished in amount." (e) The alveolar ventilation could be increased approximately eightfold when the CO_2 per cent in the inspired air was raised from 0.03 to 7.66 per cent, the alveolar CO_2 increasing from 5.62 to 8.45 per cent.

Since most of the above observations were rapidly confirmed, the regulation of ventilation by respiratory center P_{CO_2} during ordinary activity and exercise was accepted by almost all physiologists until quite recently despite the many assumptions and indirect evidence. This situation was admirably summed up by Gesell as follows: "If ever there was a connection firmly entrenched in physiology it was the monopoly of the chemical control of breathing by the respiratory center. Based as it was on circumstantial evidence, it proved to be one of physiology's outstanding creeds—central stimulation was simply taken for granted. Indirect evidence was accepted as direct proof. Statements going unchallenged were eventually accepted as facts."[15]

Direct measurement of arterial P_{CO_2} during exercise shows little or no increase in P_{CO_2} during mild exercise,[6] a slight increase during moderate exercise,[21, 25] with a definite decrease below resting values at more severe levels of work.[6, 27] Following heavy work the P_{CO_2} may continue to decline during the recovery period. These variations in ventilation and pH, are shown in FIGURE 5.

With Haldane's explanation for the divergence in ventilation/alveolar P_{CO_2} ratios during rest and exercise, the measurements of venous blood from the head are of great interest. Few data have been obtained during exercise but the available figures[6, 27] indicate a slight decrease in P_{CO_2}, a remarkably constant pH and a constant A-V oxygen difference during mild and severe exercise, which fails to lend support to the notion of a disproportionate increase in respiratory tissue pCO_2 as a cause for exercise hyperpnea. These observations likewise diminish the probability of a significant decrease in blood flow to the respiratory center during exercise, as proposed by Gesell.[14]

In summary, the most direct evidence available indicates that the arterial pCO_2 may be unchanged in mild exercise; it is slightly increased during mild-to-moderate exercise, and



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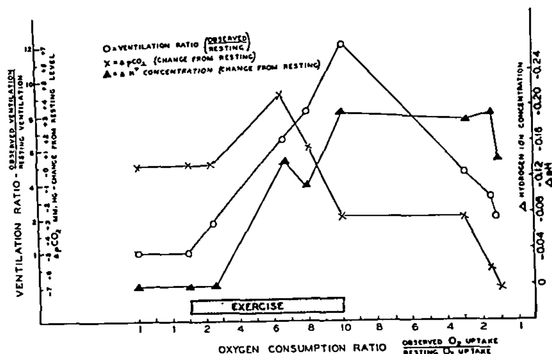
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Fluoroscopic Estimation of Ventilatory Function

By JOHN H. SEABURY, M.D.

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FLUOROSCOPY provides important information on the dynamics of breathing, especially in problems of pathophysiology that disturb normal ventilation or distribution of air in the lungs The examination is a moving picture of the chest, showing how the diaphragm, abdominal muscles, intercostal musculature, the accessory muscles of respiration and ribs participate in the act of breathing. It will reveal the differences in lucency of the two lungs and parts of each lung, and thus more clearly define the interpretations made from "still" roentgenograms Abnormal movements of the vascular hili and midline structures may give evidence of certain differences in intrapleural and intrapulmonary pressures between the two hemithoraces. With reference to the hilar structures and lung markings in the lateral third of the lung field, it is possible with fluoroscopy to gain information about the status of the pulmonary vascular tree The procedure may be invaluable in prognosticating postoperative difficulties in a particular type of surgical procedure. It is not considered as a substitute for the physiologic laboratory but, rather, another tool for exploring physical phenomena in the light of laboratory testing

The types of air-containing spaces within the lung or pleural space may be determined by using a series of simple maneuvers during fluoroscopy The probable effect on ventilation of abnormal conditions and certain pathologic processes in the parenchyma can be estimated to a considerable extent by noting the degree of aeration and movement of the lung adjacent to such diseased areas.

In attempts to teach medical residents the estimation of ventilatory function by fluoroscopy, greatest success has been achieved with those students who participated in the pulmonary function measurements in the Lung Station. The best possible training (for the fluoroscopic estimation of ventilatory function) is study of the patient during laboratory investigations of pulmonary volumina, inspecting the spirograms, and using fluoroscopy prior to bronchospirometry. At the conclusion of fluoroscopy, a percentage estimation of the distribution of ventilatory function should be written in the record for comparison with the values determined by bronchospirometry. After the period of training, one will find that the fluoroscopic estimations of percentage distribution of ventilatory function will seldom differ by more than 10 per cent from the values obtained by bronchospirometry However, estimation of oxygen uptake by the two lungs cannot be determined by fluoroscopy with this degree of precision In the Lung Station directed by the author, the distribution of ventilatory function is determined by fluoroscopy rather than bronchospirometry in all cases except borderline surgical risks and in certain patients with special problems requiring the measurement of oxygen uptake

Preparation for fluoroscopic study is simple, but important Accommodation is secured by wearing red plastic goggles for thirty minutes and then sitting in total darkness for five minutes prior to the study The goggles (Willson monogoggles) may be obtained from any x-ray supply firm. Fluoroscopy should never be performed without the protection of apron and gloves. If fluoroscopy is done frequently, a film badge should be worn at the top of the apron in order to detect unnecessary radiation hazard.

Fluoroscopic estimation of ventilatory function is undertaken with the patient in the standing position, whenever possible, the dorsal position is preferred to the "drooped-over" sitting posture frequently assumed by patients in a weakened condition Patients should be naked to the waist, or they may wear a simple gown. All requirements for the examination should be indicated to the patient before the room is darkened so as to avoid undue x-ray

exposure. The type of breathing is described, demonstrated and practiced. Next, the patient is asked to stand with his back flush against the x-ray table, and the fluoroscopic screen is adjusted just in front of the anterior chest. It is important to mention at this time that the body movements should occur easily and always under the guidance of the examiner's hand.

In fluoroscopy of the average adult, the control panel is set at 80 KV and 3.5 milliamperes Adequate observation of diaphragmatic movement can be obtained at 60 KV, but this may be quite unsatisfactory for the remainder of the routine study. The x-ray tube should be properly framed so that scatter over the screen holder poses no unnecessary hazard. Whenever attention is directed from one area to the next, exposure should be interrupted, at least briefly.

After a rapid survey of both full lung fields on the fluoroscopic screen to assure normal positioning and to note the presence or absence of gross abnormalities of cardiomediastinal position, the movements of the diaphragm are studied.

Functionally, there are two diaphragms, one beneath each lung In the present discussion, they will be so considered. With the screen framed to include a small strip beneath each diaphragm and a slightly larger segment of lung above the diaphragms, the patient is observed during quiet breathing. The patient should be asked to take deep breaths, in and out, without hesitation between inspiration and expiration. After one or two such breaths, the patient is requested to breath deeply and then *to blow out* forcefully and rapidly. During these three types of breathing each diaphragm should be observed simultaneously for range and rapidity of descent and ascent, synchronization and smoothness of motion, and to note changes in basilar lucency during inspiration and expiration

Experience will teach that some perfectly normal people do not use their diaphragms to any significant degree during quiet breathing When this is observed, the fact should be noted. On the other hand, the patient with a high degree of expiratory obstruction, as in chronic obstructive emphysema, may exhibit a greater range of diaphragmatic motion during quiet breathing than during forced breathing.

Expiratory obstruction produces prolongation of diaphragmatic ascent. When obstruction is severe, the diaphragm is immobilized during the initiation of expiration, or may descend slightly and then rise slowly to a limited degree. With marked obstruction, there usually is an increased lucency above the diaphragm during the initial phase of expiration, evidence of expiratory trapping Obstruction to expiration reduces the maximum breathing capacity much more than it lowers the vital capacity. If obstruction is unilateral, or predominantly so, the observation is very important in considering the distribution of ventilatory function.

Diffuse interstitial pulmonary fibrosis is usually recognizable in roentgenograms The fluoroscopic picture is not striking and requires experience to recognize The entire lung fields are reduced in lucency and the estimation of intrapulmonary movement is difficult. The *range* of diaphragmatic motion is reduced. *Duration* of inspiratory descent may be shortened or prolonged relative to expiration, depending on how "tight" or how noncompliant the lung has become. Duration of expiratory ascent of the diaphragms is variable but usually normal or rapid. Minor degrees of pulmonary fibrosis are not recognizable fluoroscopically unless fibrosis is sharply lobar or segmental.

Prolongation of inspiratory descent of the diaphragm is an infrequent observation. It is overlooked often in patients with loss of compliance, even during deep breathing Both inspiratory prolongation and retardation are generally evident in the presence of a large intrabronchial obstruction or stenosis of one or more major bronchi.

In addition to alterations in range and speed of diaphragmatic motion, the synchronization of the two diaphragms is quite informative. In certain cases the phenomenon of dyskinetic movement of one or both diaphragms may be encountered. This type of movement is observed only with deep breathing, particularly in rapid breathing. The reason for dyskinesia is not always apparent It may be related to

old inflammatory processes or to impaired innervation of one portion of the diaphragm; *it may follow encephalitis In some instances* it is due to abnormalities of the costal portion of the diaphragm This part of the diaphragm arises from a series of quite variable slips from the lower ribs; and it is possible that some of the lower intercostal nerves contribute to the motor innervation of the marginal portion The author has noted that dyskinetic diaphragmatic motion occurs more frequently in obese patients than in others It has been possible to control the disturbance by relatively simple instructions in breathing, an important factor because the condition, if persistent, greatly reduces maximum breathing capacity

Fixation of one part of a diaphragm, usually due to old inflammatory disease, may result in a "hinge" type of diaphragmatic movement. It may involve either the central portion of the diaphragm or the lateral third or half As a general rule, the unrestricted part of the diaphragm moves quite normally, and the condition may be unimportant functionally

Whenever the diaphragm appears to be immobilized, or moves very little during quiet breathing, one should determine whether it is fixed, paralyzed or paretic A completely paralyzed diaphragm usually ascends slightly during inspiration and descends with expiration as

TABLE 1.—*Check List for Examination of the Diaphragm*

Note position and contour of each diaphragm
- high? rounded?
- low? flattened?
- tenting?

Note motion range, speed, and equality during quiet and deep breathing and sniff
- Are descent and ascent similar in duration? equal right and left?
- Is direction of motion normal or paradoxical?
- If deep expiration is prolonged, is it relatively less so during quiet breathing? is it equally so on both sides?
- Is range of motion normal?
- If one diaphragm or portion of one is severely restricted, fixed, or paradoxical, observe in lateral or oblique projection as well as A-P

the patient breathes quietly This is called "paradoxical motion" It is usually accentuated *during deep breathing*. The phenomenon is best observed when the patient takes a sudden, forceful inspiration through the nose (sniff). The paretic diaphragm, on the other hand, may show a small range of normally directioned motion during quiet breathing and appear immobile or slightly paradoxical with deep breathing

Fixation of the depressed diaphragm during expiration, with apparent lowering of the thorax against the fixed diaphragm, is often observed in patients with advanced obstructive emphysema Either supradiaphragmatic or subdiaphragmatic inflammation may greatly *restrict or actually fix the diaphragm at a normal* or elevated position In these situations, "sniff" will result in either normally directed movements or none at all.

If the diaphragm appears immobile even during the act of sniffing, deep breathing should be noted in the lateral position with the diaphragm in question rotated close to the screen. In patients with recent or old anterodiaphragmatic pleuritis, the anterior half of the diaphragm may be fixed whereas the posterior portion moves freely The condition could be overlooked unless the patient is examined in an oblique or lateral position as described

TABLE 1 summarizes questions to be answered during fluoroscopic examination of the diaphragm In a training period it is useful to run through these aloud

On completing the studies of the diaphragm, attention should be directed to movements of the ribs and peripheral lung markings The horizontal screen is used as previously with the vertical aperture adjusted to include approximately 2 to 3 intercostal spaces Costal movements directly above the diaphragm are first observed, one should glance quickly at the relative motion of the right and left sides. Costal motion is normally greatest at the base of the lung and is best observed during deep breathing. Movement of the ribs is normally greatest anterolaterally and laterally and best noted with the anterior thorax rotated against the screen

The mid and upper lung fields are observed

in the same manner. If no abnormalities such as cysts are present, examination of intercostal breathing and the peripheral lung markings is very brief. In patients with neuromuscular disorders, such as poliomyelitis, the mechanics of breathing may depend largely on elevation of the anterior thorax by the accessory muscles of respiration. In these disorders one may observe also rather major differences in costal motion between the two hemithoraces and between upper and lower chest. Where intercostal breathing is the principal means of ventilation, more attention is paid to movement in the three lung fields, carefully comparing the two sides

During the examination of peripheral lung fields, one is usually aware of increasing lucency with deep inspiration. As mentioned previously, lucency during the two phases of breathing should be noted and compared side by side. Old pleural disease may obscure the "lighting-up" process during deep inspiration, particularly over the upper lung field. This should be recorded, but it should be remembered that apical pleural disease may have a minor influence on pulmonary ventilation, particularly if breathing is predominantly diaphragmatic. Differences in lucency must be interpreted with reference to the appearance of the chest in a current radiogram. Lucency is always decreased in inflammatory and congestive processes Alterations in lucency at the periphery may be related to pathologic processes such as pleural effusion or disease of the extrapleural thorax. One cannot interpret the effect on function unless these abnormalities are correctly identified Solid lesions in the peripheral lung fields rarely affect ventilatory function significantly unless they are large One may wish to observe the movements of the lung markings about such solid lesions; also note attachment to the pleura, or the effect of a Valsalva maneuver on the size of the lesion at the time of estimation of ventilatory function These are diagnostic problems and not pertinent to the present chapter.

Very obese people not only present problems in the study of pulmonary lucency in deep breathing but also frequently require increased kilovoltage for adequate visualization It is common to observe in the obese very limited intercostal breathing.

After examination of the ribs and peripheral lung markings, the midline structures should be studied. With the patient still facing the examiner, the fluoroscopic screen is adjusted to full vertical aperture. The horizontal field is reduced to include a small strip of lung on each side of the heart, with an adequate view of the vascular hili. With this adjustment the trachea, mediastinum, hili and heart should be visualized during deep breathing and short, forced inspiration and expiration.

In the normal individual, there is elongation and narrowing of the midline structures during deep inspiration. The hilar markings, particularly the inferior ones, elongate and fan out with descent of the diaphragm. There may be some rotation of the cardiac apex between deep inspiration and deep expiration, but the midline structures do not shift laterally During forced expiration, the mediastinum widens and the hilar vessels return to a central position and are then compressed.

In the consideration of function, the most important abnormality of the midline structures which may be observed during deep breathing is shift to either side. In the absence of fixation due to inflammatory or neoplastic disease, the structures will shift whenever there is a significant degree of inequality of the intrathoracic pressures The mediastinum will always shift toward the hemithorax with the lower intrathoracic pressure.

When shift of the midline structures is observed, the examiner should record the direction and amount of shift and the phase of breathing during which it occurs. If shift is noted during deep inspiration, one should observe whether the structures return to the midline during expiration or swing to the opposite side (pendulum movement).

Obstruction of a large bronchus sufficient to reduce the flow of air on deep inspiration will result in shift of the mediastinum toward the obstructed side. Such degrees of obstruction usually produce relatively positive intrapulmonary pressure in the affected lung during forced expiration, resulting in shift of the mediastinum to the opposite side. Lesser de-

grees of bronchial obstruction, particularly when unassociated with bullae or cysts, are not always reflected by shift of one or more of the midline structures Short, sudden, and forceful inspiration is often most revealing

Major atelectasis or lobar fibrosis may be associated with displacement of the midline structures toward the involved side, even during quiet expiration Under such circumstances, the initial screening observations of the chest will reveal the displacement, which will be considerably increased during deep inspiration

Contralateral shifts of the midline structures during forced expiration may be produced by centrally located, ball-valve obstructions such as occur with large bullae and some cysts

The reason for shift of the midline structures and its functional consequences must be determined in the light of the complete fluoroscopic examination. For example, pendulum movements of the mediastinum may be observed in the presence of a paradoxical diaphragm; and shift of the mediastinum due to centrally located ball-valve bullae is associated with alterations of the peripheral lung markings and rotational movement of the hilar markings. Small to moderate shifts due to lobar fibrosis are not nearly as important in altering ventilation as similar shifts due to bronchostenosis Obstructive disease greatly reduces the maximum breathing capacity TABLE 2 summarizes the procedure for examining the midline structures

TABLE 2—*Examination of the Midline Structures*

Open screen to full vertical aperture and narrow horizontally to observe during quiet and forced breathing
- the trachea
- mediastinum
- hili
- heart
  - On deep inspiration midline structures normally elongate if diaphragm is functioning, and remain in midline
  - Forced expiration shortens the midline structures, compresses the hili, may rotate the heart slightly, but does not produce displacement from the midline

If structures shift to one side
- Note direction and amount of shift, and phase of breathing during which it occurs (e.g., "Mediastinum and heart shift to right about 2 cm with deep inspiration ")
- Note whether structures return to midline or swing to opposite side during opposite phase of breathing
- Note in sequence the following in relation to midline shift to help explain its cause
  - diaphragmatic motion
  - costal motion
  - relative width of each hemithorax
  - differences in lucency of upper and lower fields on both sides
  - abnormal hilar and perihilar markings and movements
  - differences in peripheral lung markings

The author prefers to examine each hilus separately since much better visualization of the vessels is possible with a smaller field Information of comparative value has already been obtained during the examination of the midline structures.

The range of diaphragmatic motion profoundly affects hilar movement. This movement involves elongation and fanning during descent of the diaphragm and is far greater in the inferior hilus than in the superior Whenever diaphragmatic motion is reduced, for whatever cause, movements of the vascular hilus are likewise limited Increased intrapulmonary pressure, such as occurs in advanced obstructive emphysema, produces a vertical elongation and flattening of the hilar vessels. Pulmonary fibrosis restricts movement of the hilar vessels as well as the diaphragm when fibrosis is diffuse The superior hilus may be elevated by fibrosis in the upper lobe or by atelectasis of this lobe in the presence of apical pleuritis Elevation or depression of the hilus may be the only fluoroscopic evidence of segmental atelectasis Straightening and relative fixation of the superior hilus is often observed following pleural symphysis over the upper lobe.

Rotational movement of hilar vessels has already been mentioned It is most commonly seen adjacent to tension air spaces, central neoplasms, and atelectasis Except to indicate regional differences in intrapulmonary pressures or compliance, its importance is more diagnostic than functional.

The degree of prominence and pulsation of the pulmonary vessels are noted at the time of study of the hili. Abnormal pulsation of

hilar vessels may be due either to abnormalities of the pulmonary circulation or to intracardiac abnormalities. Intracardiac abnormalities usually give rise to significant alterations in cardiac contour by the time that pulmonary hypertension becomes evident, although this is not always true in mitral stenosis. Pulmonary hypertension may develop in advanced obstructive emphysema where it may be striking because of increased lucency of the lung and the more vertical disposition of the hilar vessels. These considerations are not properly a part of the estimation of ventilation, but are very pertinent to the status of the pulmonary circulation and the operative risk if surgery is being contemplated. Whenever there is evidence of pulmonary hypertension in the absence of serious ventilatory dysfunction, the fluoroscopist should suggest that special studies be undertaken for diagnosis and evaluation.

Definite reduction in the size and density of a hilus, such as occurs in major pulmonary artery thrombosis and pulmonary stenosis, is sometimes seen. This is usually associated with abnormal lucency of the area of lung supplied by these vessels. A considerable reduction in hilar vascularity, particularly when confirmed by appropriate roentgenograms, is a clear note of warning to the fluoroscopist interested in pulmonary function. Such patients may have *great disparity between the distribution of* ventilatory and respiratory (O_2 uptake) function. Bronchospirometry should be advised. Examination of the hili is summarized in TABLE 3.

The fluoroscopic study of abnormal, air-containing spaces within the lung is concerned with diagnosis and estimation of ventilatory function. The principal information gained is classification of the space according to the type of bronchial communication. A freely communicating cyst, as a sequelae of a lung abscess or tuberculous cavity, may show no significant change in size or shape during deep breathing if the wall is thick. Indeed, it may closely resemble an air-containing cyst with no bronchial communication. However, if the situation is not complicated by broadly adjacent pleural symphysis, the freely communicating cyst will increase in size during a Valsalva maneuver and

TABLE 3.—*Examination of the Hili*

Observe each hilus separately:
- form of superior and inferior divisions
- mobility
- prominence
- pulsations

Reduced mobility of hilar markings may be due to:
- decreased diaphragmatic motion
- pulmonary fibrosis
- inflammatory or neoplastic fixation
- *apical and subapical pleural symphysis* (superior hilus)
- pulmonary hypertension

Compression of hilus during expiration may occur when expiratory trapping is marked.

Rotational movement of hilar markings may be due to:
- central fixation (e.g., neoplasm), periphery free
- segmental atelectasis
- marked differences in intrapulmonary pressures between adjacent segments (e.g., tension cyst)

decrease in size during the Müller maneuver. A cyst without bronchial communication will not be so altered, but during forced expiration or the Valsalva maneuver, some condensation of lung markings may be seen around its margin. Thin-walled cystic spaces with free bronchial communication visibly decrease in volume during forced expiration. It is known that large cystic spaces with free bronchial communications are often associated with distinct elevation of the resting minute ventilation which *may aid in classification of the cyst.*

The recognition of large intrapulmonary spaces with free bronchial communication is important functionally because they represent considerable expansion of the dead space. The presence of such spaces is frequently an indication for an attempt at surgical correction.

Air-containing spaces, principally giant blebs and bullae, which compress the adjacent lung are usually recognized at fluoroscopy. Evidence of compression is seen in the adjacent lung during forced expiration, often emphasized by the abnormal position and visibility of an interlobar fissure. They increase in lucency by comparison with the surrounding lung during deep expiration, and they may produce expiratory deviation of the mediastinum toward the uninvolved side. As mentioned, they may alter the normal movement of the hilar vessels if they are in proximity to them.

Large ball-valve air spaces at the base of the lung are easily recognized during forced expiration. When located laterally, they restrict the ascent or actually depress the diaphragm, widen the intercostal spaces, and remain abnormally lucent. Medial ones are more likely to cause a shift of the midline structures and compress or rotate the hilar vessels Abnormal expiratory lucency and marginal compression of lung markings are often noted best in the oblique projections

Ball-valve air spaces impair ventilatory function much more than cysts with a free bronchial communication Both increase the dead-space ventilation, but ball-valve structures greatly reduce the maximum breathing capacity Recognition and estimation of size are important in approaching the distribution of ventilatory function and making recommendations for surgery.

With proper routine, the exposure time for fluoroscopy can be limited to one minute for the average patient and two minutes for difficult problems such as the nature of cysts The fluoroscopic examination should be preceded immediately by physical examination of the chest, inspection of the spirograms, and review of the values for the resting minute ventilation, maximum breathing capacity, and vital capacity. This information together with a full understanding of all of the clinical data are essential if one is to derive all possible information from a single fluoroscopic study The fluoroscopic examination should be conducted prior to the administration of bronchodilator drugs

A written record of all fluoroscopic findings should be made immediately following the examination. When the observations have been recorded, the percentage distribution of ventilatory function between the lungs or lobes may be estimated. An interpretation of the findings is important but is not a substitute for a precise record of fluoroscopic observations. These observations are of great value in follow-up cases and whenever records are to be reviewed or decisions made in surgical conference.

During the estimation of ventilatory function, the clinical fluoroscopist may obtain useful knowledge about the nature of intrapulmonary densities and the probable resectability of many neoplasms. Although not a part of the fluoroscopic estimation of ventilatory function, such ancillary information is best obtained during the routine observations utilized for assessment of function

Caution should be exercised in estimating ventilatory function by fluoroscopy in those patients who have had major chest surgery months or years prior to examination The effects of pleural restriction may be greatly overestimated On the other hand, postoperative fixation of the mediastinum and restriction of the diaphragm may obscure evidence of expiratory obstruction This is particularly true following thoracoplasty Unilateral chest surgery may produce a significant disproportion between ventilation and oxygen uptake in the underlying lung If further surgery is contemplated, bronchospirometry should be performed in all patients whose total function suggests the possibility that pulmonary crippling may result from surgery

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The Compartments of the Lung Volume and Their Physiologic Significance

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THE compartments of the lung volume are essentially anatomic measurements, but alterations in the relative size of these compartments often reflect physiologic disturbances. It is of both clinical and physiologic importance to measure these compartments, to know the normal values, and to be able to interpret the deviations from such normal values.

The terms used for the various compartments and subdivisions are those agreed upon in 1950 by a group of American physiologists[42] and now widely accepted These terms, their abbreviations and definitions are shown in TABLE 1. FIGURE 1 is a diagram of the four primary lung volumes, showing successive increments from the position of maximal expiration to that of maximal inspiration. Figure 2 presents the lung volumes depicted spirographically with A representing the primary compartments and B the special subdivisions used in pulmonary function testing The term "volume" refers to one of the four primary compartments of the total lung capacity. The term "capacity" relates to pulmonary function testing procedures, each "capacity" is made up of two or more of the primary "volumes"

When a subject changes his position from standing to recumbent, the changes in the lung volumes show great individual variation between the upright and the recumbent positions.[8] This difference often cannot be detected. We have frequently found identical vital capacity values for the standing and recumbent positions both in normal subjects and in patients. Body position does affect the resting expiratory level as illustrated in FIGURE 3. In the recumbent position the diaphragm is somewhat elevated so that the resting expiratory level as seen on the spirogram is low and the inspiratory capacity (IC) is as much as 4 times as large as the expiratory reserve volume (ERV) In the upright position the weight of the abdominal viscera pulls the diaphragm to a more inspiratory position with a higher resting expiratory level. This is reflected by an increase in functional residual capacity (FRC) and by decrease in the IC/ERV ratio of 2 to 1 or less.

In FIGURES 2 AND 3 the resting tidal volume is depicted. Actually, the tidal volume in any person will vary with the level of activity FIGURE 4 illustrates changes in tidal volume during exercise as the work output and ventilation volume increase. The increase in tidal volume is predominantly at the expense of the *inspiratory reserve volume* until the exercise becomes severe at which time the tidal volume also encroaches upon the expiratory *reserve* volume.

THE VITAL CAPACITY AND ITS SUBDIVISIONS

History and Normal Values

The oldest and most thoroughly studied test of lung function is the vital capacity (VC). John Hutchinson in 1846[24] clearly delineated the compartments of the lung volume, described and defined the vital capacity, and devised the first spirometer for its measurement. Hutchinson measured the vital capacity in 2,000 healthy males, in 26 "girls" and in 360 "diseased cases." He recognized that the vital capacity varied directly with height and with chest expansion and inversely with age.

The simplicity and rapidity with which vital capacity could be measured led to an abun-

TABLE 1 —*Terms, Definitions and Abbreviations for Divisions of the Lung Volume*

Primary Compartments of the Lung Volume				Special Divisions for Pulmonary Function Tests			
Standardized Term	*Abbreviation*	*Definition*	*Previous Terms*	*Standardized Term*	*Abbreviation*	*Definition*	*Previous Terms*
Inspiratory Reserve Volume	IRV	Maximal volume that can be inspired from end tidal inspiration	Complemental air, Complementary air, Inspiratory capacity minus tidal volume	Inspiratory Capacity	IC	Maximal volume that can be inspired from the *resting expiratory* level	Complemental air, Comple*mentary* air
Tidal Volume	TV	Volume of gas inspired or expired during each respiratory cycle	Tidal air	Vital Capacity	VC	Maximal volume that can be expelled from the lungs by a forceful effort following a maximal inspiration	Vital capacity
Expiratory Reserve Volume	ERV	Maximal volume that can be expired from resting expiratory level	Supplemental air, Reserve air	Functional Residual Capacity	FRC	Volume of gas in the lungs at the resting end-expiratory level	Functional residual air, Midcapacity, Normal capacity
Residual Volume	RV	Volume of gas in the lungs at end of maximal expiration	Residual air, Residual capacity	Total Lung Capacity	TLC	Volume of gas in the lungs at the end of a maximal inspiration	Total lung volume

dance of subsequent studies of vital capacity with tables of normal values and formulae for prediction. Peabody and Wentworth, in 1917, related the vital capacity to body surface area,[43] and Lundsgaard and Van Slyke related this measurement to the calculated thoracic volume.[31] Dreyer, in 1919,[15] disagreed with Hutchinson on almost every point and related vital capacity to body weight, body surface area, stem length and chest circumference His conclusions, however, were based on measurements made in only 16 boys and men. West related vital capacity to both body surface area and to height, and prepared quite simple prediction formulae for these relationships.[48] These were modified slightly two years later by Hewitt and Jackson [21] Myers related the vital capacity to body weight, body surface area and to sitting height, and established tables of normal standards based on these relationships.[40] Among the most well known standard prediction formulae in current use are those proposed by Baldwin, Cournand and Richards, in 1948.[1] More recent studies include those of Bateman[2], Motley[39], Needham, Rogan, and McDonald[41], Pemberton and Flanagan[44], Miller, Johnson and Wu[37], Hepper, Fowler, and Helmholz[20]; and most recently the VA-Army Cooperative Study of Pulmonary Function Testing [24] These several investigations are in essential agreement, that the vital capacity and the total lung capacity vary directly with height and inversely with age TABLE 2 outlines several of the formulae used for predicting vital capacity in normal adults. The VA-Cooperative Study of Pulmonary Function at this time would appear to offer the best prediction formula for the vital capacity in normal adult males of

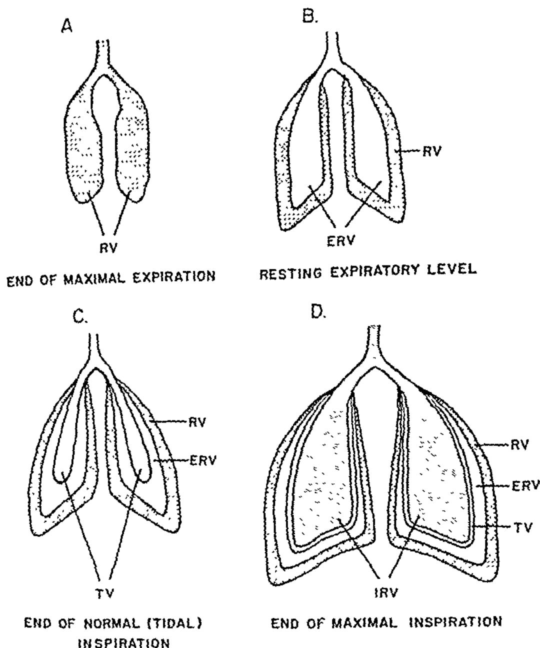


FIG 1 -- Diagram of the addition of successive compartments of the lung volume as the subject inhales from maximum expiration to maximum inspiration RV = Residual Volume; ERV = Expiratory Reserve Volume; TV = Tidal Volume, IRV = Inspiratory Reserve volume.

varying age. We have recently analyzed the results of vital capacity measurements in 475 women between the ages of 20 and 65 years[23] from which we have derived the following prediction formula.

$$VC = .041H - .018A - 2.69$$

VC = vital capacity in liters.
H = height in cm. (without shoes)
A = Age in years

This formula should be the most r
available at this time for the prediction
vital capacity in normal adult women

Technic

The vital capacity (VC) is measured b
ing the subject exhale maximally after a
mal inspiration into a suitable and ac
gas measuring device Closed circuit sp
ters of from 6 to 13½ L. capacity hav

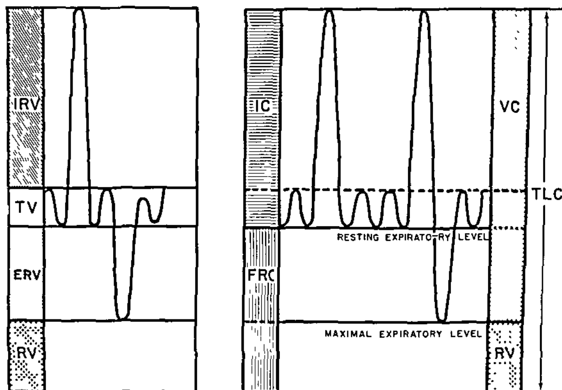


FIG 2.—Diagram of the spirometric representation of the primary compartments of the lung (*left*), and the special divisions (capacities) used in pulmonary function testing (*right*) IRV = Inspiratory Reserve Volume, TV = Tidal Volume, ERV = Expiratory Reserve Volume, RV = Residual Volume, IC = Inspiratory Capacity, FRC = Functional Residual Capacity, VC = Vital Capacity, TLC = Total Lung Capacity

most practical and widely used Although almost any such instrument is satisfactory for measurement of total vital capacity, accurate performance of the *forced vital capacity* requires an instrument of comparatively low resistance If timed expiratory volumes and expiratory flow rates are to be measured, a recording kymograph of some type should be used The most commonly employed instruments are the Collins 9 and 13½ L respirometers* although other instruments such as a recently introduced recording bellows apparatus† are entirely adequate for such measurements [24] Repeated measurements of vital capacity must be made until maximal volumes and good duplication are achieved. The VC testing procedure may be reversed by having the subject first *exhale maximally* and follow this with a *maximal inspiration*. This measurement is termed the *inspiratory vital capacity* (IVC) In normal individuals VC = IVC, but in certain types of patients IVC may exceed VC The sum of the inspiratory capacity (IC) and expiratory reserve volume (ERV) measured separately may in some patients yield a vital capacity value higher than the conventional VC measurement This is particularly true in the case of patients with asthma, emphysema or other obstructive ventilatory impairment in which trapping of air is evident

THE SIGNIFICANCE OF THE VITAL CAPACITY

The vital capacity of healthy individuals may vary as much as 20 per cent from the predicted values despite the care with which the prediction formulae were derived Thus, a single absolute measurement of the vital capacity must be at least 20 per cent below the predicted normal, before it can be regarded as subnormal. Changes in the vital capacity, however, are important regardless of the absolute value. Serial *reductions* in the vital capacity may quantitate

* Manufactured by Warren E Collins, Inc, Boston 15, Mass

† Vitalor, McKesson Appliance Company, Toledo, Ohio

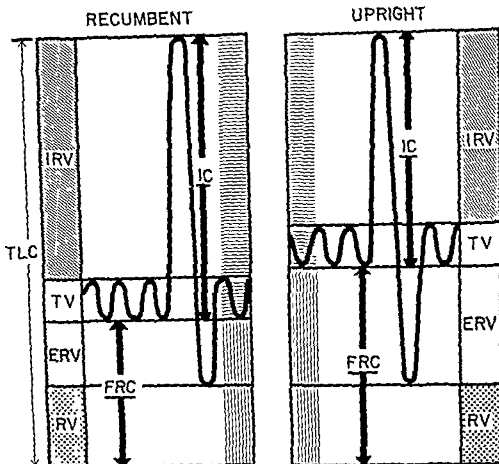


FIG 3—Spirograms of a subject in the recumbent and upright positions to show the shift in the resting expiratory level (breathing baseline) and the resulting changes in lung volumes and lung capacities Abbreviations are the same as those used in FIGURE 2

the degree of functional impairment which may ensue with progressive pulmonary disease. An increase in vital capacity, on the other hand may quantitate the degree of improvement achieved by either acute or long-term therapeutic measures

The vital capacity may be reduced by·

1. *Poor patient co-operation* or understanding
2 *An absolute reduction in functioning lung tissue* resulting from such conditions as tuberculosis, pneumonia, pulmonary fibrosis, pulmonary edema, tumors, atelectasis and surgical excision of pulmonary tissue
3 *Limitation of chest expansion* caused by tight strapping of the chest, obesity, fractured ribs, bony deformities such as kyphoscoliosis and neuromuscular diseases such as poliomyelitis, myasthenia gravis or primary muscle disorders.
4 *Limitation of diaphragmatic motion* caused by phrenic nerve paralysis, pneumoperitoneum, ascites, pregnancy or abdominal tumor
5 *Limitation of lung expansion* from such conditions as pleural effusion, pneumothroax, diaphragmatic hernia, fibrothorax or marked cardiac enlargement.
6 *Airway obstruction or loss of lung elasticity* from such conditions as asthma, emphysema, bronchitis, bronchiectasis or bronchial stenosis

The vital capacity may be reduced in so many diseases that as an isolated test it is of little or no value in the differential diagnosis of disease of the lungs or thorax. Indeed certain patients, particularly those with airway obstruction, may have a vital capacity which is within the normal range. In such conditions, however, the *forced* vital capacity always exhibits slowing, with low values for the timed expiratory volumes and the expiratory flow rates The forced vital capacity and flow rates are discussed in more detail in Chapter 37.

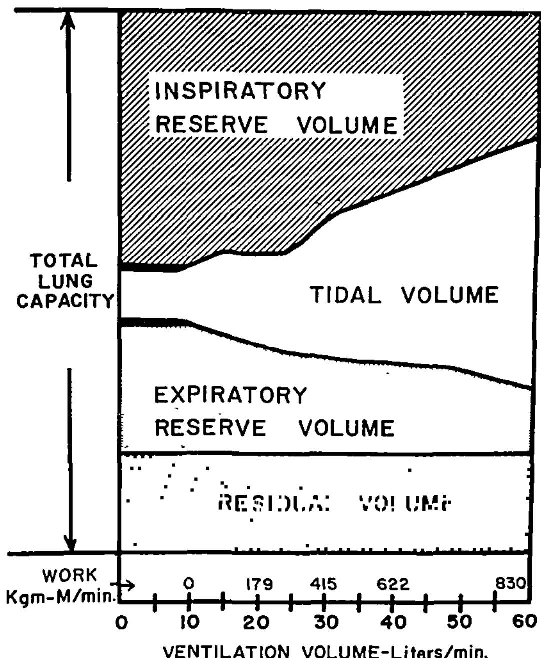


FIG 4 —Diagram showing the effect of increasing exercise on ventilation and lung volumes Most of the increase in tidal volume comes from the *inspiratory* reserve volume

RESIDUAL VOLUME, FUNCTIONAL RESIDUAL CAPACITY, AND TOTAL LUNG CAPACITY

The residual volume (RV)—the volume remaining in the lungs after a maximal expiration—is the only one of the four primary compartments of the lung volume (FIGS 1 AND 2) which cannot be measured by direct spirometry. The two major categories for indirect methods of measurements of RV include (1) gas dilution methods and (2) pressure-volume or pneumatometric methods With any of the technics, the volume of alveolar gas measured is the volume contained in the lung at the beginning of the test. If the test is begun at the moment of *maximal expiration*, the residual volume is measured. If tested at the level of *maximal inspiration*, the total lung capacity is measured Usually, however, the test is begun at the *resting expiratory level* which is more

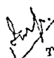


TABLE 2.—*Prediction Formulae for Vital Capacity Adult*

Author and Year	Number of Subjects	Prediction Formula	Reference Number
		Males	
West, 1920	85	(1) $VC, L = 2\ 5 \times M^2\ BSA$ (2) $VC, ml = 25 \times H_{cm}$	48
Hewlitt and Jackson, 1922	100	$VC, L = 2\ 9 \times M^2\ BSA - 1$	21
Myers, 1923	1280	$VC, ml = W_{lb} \times 21.2 + 1168$	40
Baldwin, Cournand and Richards, 1948 (supine)	54	$VC, ml = (27.63 - \ 112A)\ H_{cm}$	1
Bateman, 1950	12	$VC, ml = 873\ (H_M)^2$	2
Needham, Rogan and McDonald, 1954	102	$VC, ml. = 110\ H_{in} - 35A - 1910$	41
Pemberton and Flanagan, 1956	428	$VC, L = \ 0465\ H_{cm} - \ 0292A - 2\ 418$	0
Miller, Johnson and Wu, 1959	77	$VC, L = [\ 135\ H_{in} - 4\ 15][1 - \ 0054\ (A - 20)]$	37
Hepper, Fowler and Helmholz, 1960	76	$VC, L = \ 9\ (H_M)^2$	20
VA-Army Cooperative Study, 1960	468	$VC, L = \ 052\ H_{cm} - \ 022A - 3\ 60$	28
		Females	
West, 1920	44	(1) $VC, L = 2\ 0 \times M^2\ BSA$ (2) $VC, ml = 20 \times H_{cm}$	48
Baldwin, Cournand and Richards 1948 (supine)	40	$VC, ml. = (21\ 78 - \ 101A)\ H_{cm}$	1
Needham, Rogan and McDonald, 1954	64	$VC, ml = 100\ H_{in} - 20A - 2710$	41
Miller, Johnson and Wu, 1959	76	$VC, L = [\ 132\ H_{in} - 4\ 85][1 - \ 00105\ (A - 20)]$	37
Kory, Hamilton, and Callahan, 1960	475	$VC, L = \ 041\ H_{cm} - \ 018A - 2\ 69$	29

VC = Vital Capacity
W_{lb} = Weight in pounds
A = Age in years
M^2 BSA = Square meters, body surface area
H_{cm} = Height in centimeters.
H_{in} = Height in inches
H_M = Height in meters

constant than either maximal inspiration or maximal expiration Thus, the *functional residual capacity* (FRC—FIG 2) is measured, the *expiratory reserve volume* (ERV) is determined by spirometry and subtracted from the FRC to obtain the residual volume (RV).

The classic paper of Christie[5] outlines the history of lung volume measurements. The first gas dilution method (hydrogen) was proposed by Davy in 1800 and the pressure-volume, or pneumatometric method, was described by Pfluger in 1882.

Historical Resume of Closed Circuit Technics

Forced Breathing H_2 Dilution; O_2 Dilution

The earliest gas dilution method for measuring the lung volume employed hydrogen as the gas and required forced breathing in which the subject, after a forced expiration, takes 5 to 7 deep rapid breaths from a bag or spirometer containing a known volume of hydrogen This method was utilized with only fair success by Bohr in 1907 and Fobiesen in 1911. Subsequently, Lundsgaard and Van Slyke employed this same principle but used oxygen as the diluting gas [31]

Quiet Breathing (Measurement of FRC), H_2 Dilution, O_2 Dilution

The modern type of closed circuit gas dilution measurements date from 1923 when Van Slyke and Binger[47] described their method for measurement of the *functional residual capacity* by hydrogen dilution with a quiet breathing period of 5 to 7 minutes to allow mixing The major problems with this technic were. (1) the explosive hazard of hydrogen, (2) the unknown quantity of hydrogen absorbed and (3) the unknown quantity of nitrogen excreted by the blood

In order to avoid the explosion hazard of hydrogen Christie in 1932 introduced the *quiet breathing-oxygen dilution* technic.[5] This method was widely used until supplanted by McMichael's modification of the hydrogen dilution method[32] (later adapted by Meneely and Kaltreider[33, 34] for helium) and by the open circuit nitrogen washout technic of Darling, Cournand and Richards.[11] The latter two technics are in widespread use and will be described in detail.

Closed Circuit Helium Dilution Method for Measurement of Functional Residual Capacity

The helium dilution method of Meneely and Kaltreider[33, 34] utilizes a recording spirometer, a katharometer, a CO_2 absorber and a blower. Figure 5 is a diagram of the apparatus. The dead space of the apparatus is filled with air and can be measured by introducing a known volume of 100 per cent helium and mixing by means of the blower. The final helium concentration allows the calculation of the dead space according to the following formula

$$\textit{Instrument Dead Space} = \frac{\textit{Vol of He Added}}{\textit{Final He Conc}} - \textit{Vol He Added} \qquad (1)$$

In the helium dilution method as described initially,[33, 34] a volume of helium is added to the spirometer and the subject is connected to the spirometer A constant oxygen supply is required to replace the oxygen consumed by the subject during the testing period The breathing baseline in such cases should be maintained as nearly horizontal as possible while mixing of the helium is taking place throughout the spirometer and lungs When a stable helium reading is obtained, mixing of the helium is considered complete. The FRC is calculated from the following equation

$$FRC = \frac{\textit{Vol He added}}{\textit{Final He conc}} - \textit{Vol He added} - \textit{apparatus dead space} \qquad (2)$$

In recent years, a simplified version of the helium dilution method has been devised [13, 35, 36, 39] After the appropriate volume of helium is introduced (1 0 to 1 5 L) into the spirometer, a line is inscribed on the paper by turning the kymograph drum by hand—termed the helium in air baseline (Fig 6) A 7 to 10 minute O_2 supply is then added (approximately 1.6 L.) and the subject is connected to the spirometer. The subject then rebreathes until his breathing baseline (Fig. 6) exactly crosses the helium in air baseline, at which time a helium reading is taken.

The volume of helium is measured on the tracing with a good millimeter ruler and not by reference to calibrations on the paper. With these values the FRC can be calculated from equation 2.

The katharometer is designed for use with a 6 volt storage battery, but with age the current output of the battery may vary and lead to errors in the measurement of helium concentration. Excellent stability which increases both accuracy and the ease of operation is achieved

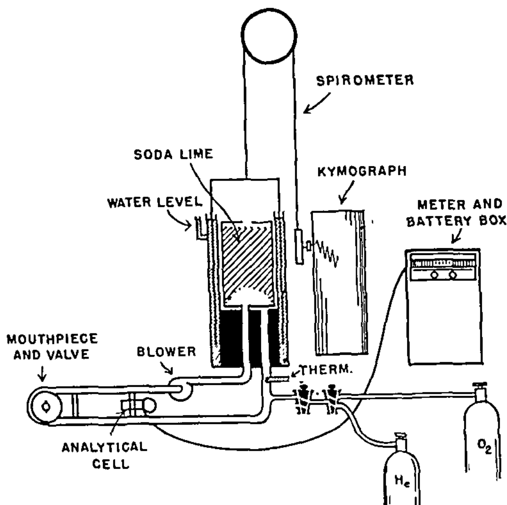


FIG 5—Schematic drawing of a simplified closed circuit helium dilution apparatus for measuring the functional residual capacity

by substituting an electronic power supply for the battery *

Certain corrections must be made in the studies The mouthpiece and valve which become part of the system during measurement are usually not included when the volume of the instrumental dead space is measured This volume, usually 10 to 15 cc., should also be subtracted from the FRC volume before temperature corrections During the period of equilibration some helium is absorbed in the tissues and blood despite the limited solubility of helium This amount has been estimated at 8 to 10 ml[4] which would cause a 100 to 110 ml. overestimate in the final FRC

* Collins Battery Eliminator manufactured by Warren E Collins, Inc , 555 Huntington Avenue, Boston 15, Massachusetts

If the patient is not connected to the spirometer at exactly the level of resting expiration, a volume greater than the FRC will be measured. A correction can be made by observing the spirographic record and subtracting the excess volume measured from the FRC volume Since helium concentration is measured by thermal conductivity (katharometer), a 1 per cent variation in the nitrogen concentration in the unknown mixture will cause approximately 25 ml error in the functional residual capacity. Since the nitrogen increment during the procedure usually approximates 3 per cent, a correction factor of approximately 75 ml has been applied in clinical use of this technic. This combined with the correction for helium absorption, 100 ml, and an additional dubious correction for RQ has been rounded to 200 ml.

Historical Resume of Closed Circuit Technics

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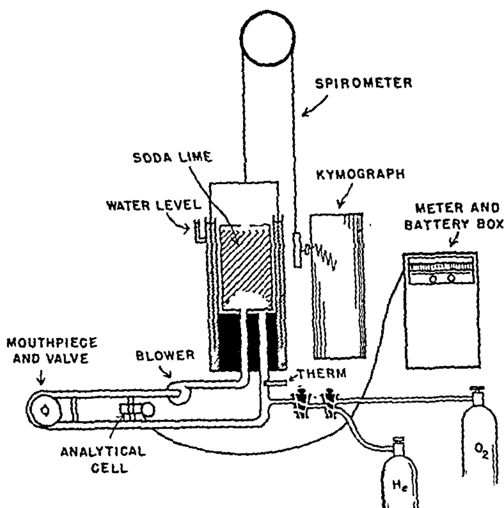


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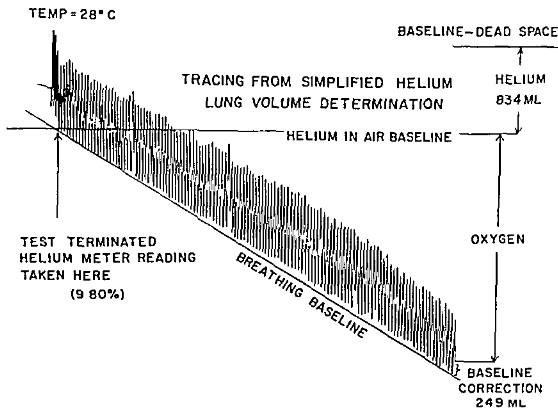


Fig 6 —Spirographic tracing from closed circuit helium dilution FRC measurement showing the helium baseline, a baseline correction for the volume measured in excess of the FRC, the decreasing volume as oxygen is consumed, the termination point where the final helium reading is made (The tracings should be read from right to left)

A detailed discussion of the correction factors for the simplified decreasing oxygen technic has recently appeared.[34]

Figure 6 is a spirometric tracing made during the simplified helium dilution procedure Here, the helium added was 834 ml and the *final helium meter reading 9 80 per cent. The* instrumental dead space was 5030 ml The calculation here using equation 2 would be as follows:

$$FRC_{ATPS} = [834/0.0980] - 834 - 5030 - 200 - 249 = 2197 \text{ ml}$$

ATPS = ambient temperature and pressure, saturated
5030 = dead space of apparatus
200 = standard correction factor
249 = baseline correction, since the subjet was connected to the helium system 249 ml above the breathing baseline (resting expiratory level)

Finally the FRC_{ATPS} is converted to the FRC at body temperature (FRC_{BTPS}) by applying a temperature conversion factor[8] For a temperature of 28 degrees (Fig 6), the BTPS conversion factor is 1 057 Thus

$$FRC_{BTPS} = FRC_{28°} \times 1.057 = 2197 \times 1.057 = 2320 \text{ ml}$$

If accurate estimations of the residual volume and total lung capacity are desired, the measurements of the *inspiratory capacity* and *expiratory reserve volume* must be done with the patient in the same position and with the same breathing baseline (resting expiratory level). These measurements are illustrated in Figure 7. The importance of this detail can be demonstrated by reference to Figure 3. If the FRC measurement is made in the recumbent position but the ERV measurement made in the upright position, the *calculated* RV would be approximately one-third of its true value

Open Circuit Nitrogen Washout Method for Measurement of Functional Residual Capacity

In contrast to the closed circuit methods which were developed over the span of 150

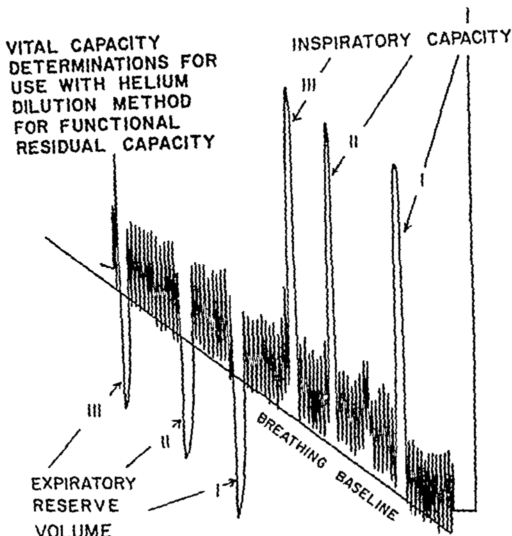


FIG 7—Spirographic tracing for measurement of inspiratory capacity and expiratory reserve volume of the subject whose FRC was measured in FIGURE 6, so that the residual volume (RV) and total lung capacity (TLC) could be accurately calculated The tracings in FIGURES 6 and 7 are made with the patient in the same position

years, the open circuit technique was first described by Darling, Cournand, and Richards in 1940[11] and has been widely used since then with only minor modifications

In this dilution technique the nitrogen in the lung is "washed out" of the lung by inhalation of pure oxygen (99 6+ per cent) and all the expired gas is collected. An assumption is made that the original alveolar nitrogen concentration can be considered uniform and at a level of 81 per cent FIGURE 8 is a diagram of the basic apparatus used in the open circuit method. The 5-way valve* is particularly convenient for this procedure. The subject breathes through the mouthpiece, M, which may, by turning the handle, be connected with sidearms A, B or C When the subject begins the test, M is connected with A through which the subject breathes room air. Meanwhile the gasometer and all the connecting tubes are thoroughly rinsed with "pure" oxygen from the tank. The breathing bag interposed provides a reservoir and allows humidification of the oxygen

After the apparatus is thoroughly rinsed, the valve handle is turned at the end of a quiet *expiration* to connect M with sidearm B and the oxygen circuit. The subject then breathes for 7 minutes, his expired gas being collected in the Tissot gasometer.

* Several satisfactory valves are available—Warren E. Collins, Inc , 555 Huntington Avenue, Boston, Massachusetts

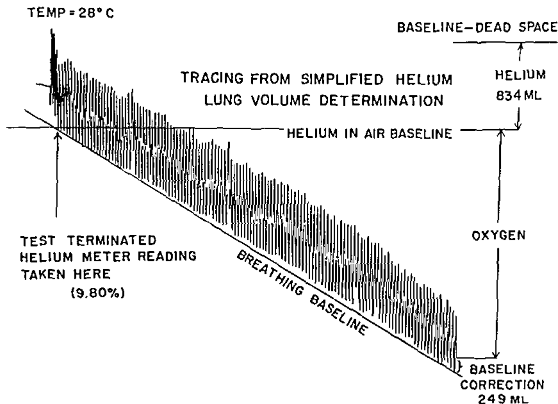


FIG 6 —Spirographic tracing from closed circuit helium dilution FRC measurement showing the helium baseline, a baseline correction for the volume measured in excess of the FRC, the decreasing volume as oxygen is consumed, the termination point where the final helium reading is made (The tracings should be read from right to left)

A detailed discussion of the correction factors for the simplified decreasing oxygen technic has recently appeared[36]

FIGURE 6 is a spirometric tracing made during the simplified helium dilution procedure Here, the helium added was 834 ml and the final helium meter reading 9 80 per cent. The instrumental dead space was 5030 ml. The calculation here using equation 2 would be as follows:

$$FRC_{ATPS} = [834/0.0980] - 834 - 5030 - 200 - 249 = 2197 \text{ ml}$$

ATPS = ambient temperature and pressure, saturated
5030 = dead space of apparatus
200 = standard correction factor
249 = baseline correction, since the subjet was connected to the helium system 249 ml above the breathing baseline (resting expiratory level)

Finally the FRC_{ATPS} is converted to the *FRC* at body temperature (FRC_{BTPS}) by applying a temperature conversion factor.[6] For a temperature of 28 degrees (FIG. 6), the BTPS conversion factor is 1.057 Thus

$$FRC_{BTPS} = FRC_{28°} \times 1.057 = 2197 \times 1.057 = 2320 \text{ ml}$$

If accurate estimations of the residual volume and total lung capacity are desired, the measurements of the *inspiratory capacity* and *expiratory reserve volume* must be done with the patient in the same position and with the same breathing baseline (resting expiratory level). These measurements are illustrated in FIGURE 7. The importance of this detail can be demonstrated by reference to FIGURE 3 If the FRC measurement is made in the recumbent position but the ERV measurement made in the upright position, the *calculated* RV would be approximately one-third of its true value.

OPEN CIRCUIT NITROGEN WASHOUT METHOD FOR MEASUREMENT OF FUNCTIONAL RESIDUAL CAPACITY

In contrast to the closed circuit methods which were developed over the span of 150

tus, the gases available, and the principles of gas exchange, certain corrections must be applied, each of which slightly alters the basic equation:

1 The dead space of the gasometer and all connecting tubing is completely rinsed with pure oxygen at the outset. Thus, the nitrogen washed out of the lungs during the test is diluted in volume of the *apparatus dead space* (*DS*) in addition to the volume of expired gas (V_E). Equation 4 is modified accordingly:

$$V_{FRC}(81 - F_{A_{N_2}}(final)) = (V_E + V_{DS})F_{E_{N_2}} \quad (5)$$

V_{DS} = volume of the apparatus dead space

2 Since it is more economical to use commercial grades of oxygen which may contain as much as .4 per cent nitrogen, it is necessary to analyze nitrogen concentration in the O_2 tank. Equation 5 must then be corrected for the N_2 concentration in this *inspired* gas ($F_{I_{N_2}}$):

$$V_{FRC}(81 - F_{A_{N_2}}(final)) = (V_E + V_{DS})(F_{E_{N_2}} - F_{I_{N_2}}) \quad (6)$$

3 Since nitrogen is a diffusible gas, the blood and tissue nitrogen is in equilibrium with the alveolar nitrogen. As "pure" oxygen is breathed, the alveolar nitrogen tension falls and nitrogen is excreted from the blood and tissues to enter the alveolar gas. The quantity of this nitrogen excretion is termed the "C" correction, it has been found to vary with body size according to the linear relation[18]

$$\text{"C" ml} = (M^2 BSA \times 96.5) + 35$$

$M^2 BSA$ = the square meters of body surface area

This "C" correction must be subtracted from the right hand side of the equation.

Rearranging equation 6 and inserting the "C" correction provides the final equation

$$V_{FRC_{37°}Dry} = \frac{(V_E + V_{DS})(F_{E_{N_2}} - F_{I_{N_2}}) - \text{"C"}}{81 - F_{A_{N_2}}(final)} \quad (7)$$

In order to keep the terms consistent it is necessary to convert the two gas volumes V_E and V_{DS} to *dry gas at 37 C* by the following formula.

$$V_{37°Dry} = V_{ATPS} \times \frac{P_B - P_{H_2O(t)}}{P_B} \times \frac{273 + 37}{273 + t} \quad (8)$$

V_{ATPS} = the gas volume at ambient temperature and pressure, saturated with H_2O

P_B = barometric pressure

$P_{H_2O_{(t)}}$ = vapor pressure of water at temperature t (from Table 6)

t = ambient temperature.

Since the gas analyses are usually done on dry gas and the other lung volume measurements are corrected to BTPS (body temperature and pressure, saturated), the volume of the FRC, dry at 37 C is converted to BTPS by the following equation

$$V_{FRC_{BTPS}} = V_{FRC_{37°}Dry} \times \frac{P_B}{P_B - 47} \quad (9)$$

The three nitrogen concentrations ($F_{A_{N_2}}$, $F_{E_{N_2}}$ and $F_{I_{N_2}}$) may be analyzed with the Van Slyke-Neill apparatus, the Scholander micrometer gas analyzer, the nitrogen meter, or, as recently reported, the gas chromatograph.[19]

The nitrogen washout technic has several sources of error of greater or lesser importance. The usual method as described above does not provide a record of the point at which the subject was connected to the oxygen circuit. If the nitrogen washout is begun at a point other than the breathing baseline (FRC level), an error of up to 300 ml may be introduced. This can be avoided by substituting for the Tissot gasometer a large (150 to 200 L.) Donald-Christie bag-in-box[14] attached to a conventional spirometer for collection of the expired gas. An alternative method is the insertion of a smaller bag-in-box system in the room air circuit (*A*, Fig. 8), so that a spirometer may record the breathing pattern continuously up to the point where the subject is turned into the oxygen circuit. Either method will provide a clear indication as to the breathing level at the start of the test.

The bag-in-box system used in this manner allows measurement of the inspiratory capacity and the expiratory reserve volume just before the nitrogen washout period. This will, at the same time, provide the necessary correlation between the breathing baseline for the FRC determination and for the compartments of the vital capacity.

The several sources of inaccuracy in the

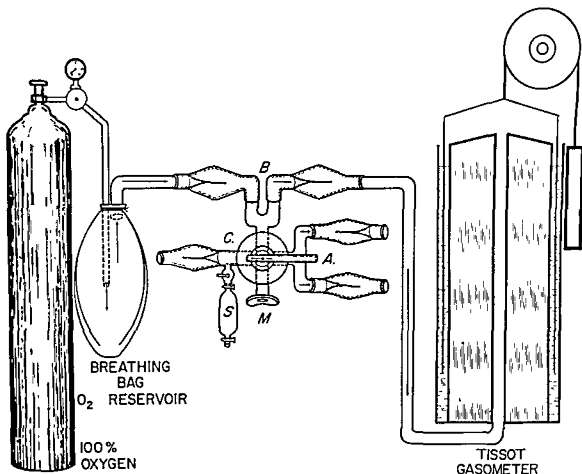


FIG 8—Schematic drawing of the open circuit nitrogen washout apparatus for the measurement of the functional residual capacity A = a circuit to permit the patient to breathe room air until the test is begun (A bag in a box system with a recording spirometer may be attached to this circuit to permit the recording of the level of respiration when the test was begun) B = the nitrogen washout circuit permitting the subject to breathe 100 per cent oxygen C = a circuit to permit the collection of a final alveolar gas sample in tonometer (S) M = the mouthpiece through which the subject breathes

At the end of the 7 minute breathing period the valve handle is turned at the end of quiet *inspiration* to connect M with sidearm C The subject is asked to exhale all of this breath, most of which passes through the one-way valve The end expiratory gas is trapped, however, as the handle is quickly turned back to sidearm A and room air breathing Then this *final end expiratory* (alveolar) gas is drawn into sampling tube S for measurement of the final alveolar N_2 concentration.

The calculation of FRC measured by the open circuit technique utilizes the basic dilution equation:

$$V_{FRC} \times F_{A_{N_2}}\ (initial) = V_E \times F_{E_{N_2}} \quad (3)$$

V_{FRC} = the FRC volume
$F_{A_{N_2}}$ *initial* = the fractional N_2 concentration in the alveoli at the beginning of the test
V_E = the volume of the expired gas
$F_{E_{N_2}}$ = the fractional concentration of expired N_2

Since at least a small concentration of nitrogen remains in the lungs after the washout period, the remaining alveolar nitrogen concentration ($F_{A_{N_2}}$ (final)) must be subtracted from the initial alveolar nitrogen concentration ($F_{A_{N_2}}$ (initial)). Since $F_{A_{N_2}}$ (initial) is assumed to be .81, equation 3 is modified thus

$$V_{FRC}(.81 - F_{A_{N_2}}\ (final)) = V_E \times F_{E_{N_2}} \quad (4)$$

Because of the characteristics of the appara-

It does, however, require an accurate nitrogen meter.

In the closed circuit helium technique for measuring FRC the curve of helium dilution provides a good index of gas distribution. The rate of dilution may be *exponential* indicating uniform distribution or it may be *rapid initially* reflecting the well ventilated areas and then *slower* because of the less rapid exchange with the poorly ventilated regions.

In the helium dilution technic in which oxygen is continually replaced, the helium concentration falls to an equilibrium point and levels off. Meneely and Kaltreider[34] plotted such curves and found that the equilibrium point in normal subjects did not exceed 3½ minutes. Bates and Christie have recorded similar findings with their technic.[3] In the simplified decreasing volume helium closed circuit method, helium meter readings have been made in our laboratory at 30 second intervals during rebreathing periods of from 4 to 12 minutes during determinations of the functional residual capacity.[30] As the helium first mixes in the lungs, the concentration drops sharply. When even distribution is achieved, the helium concentration begins to rise, reflecting the decrease in the volume of the spirometer system as oxygen is consumed and taken out of the system The "equilibrium point" is the lowest helium concentration recorded before the secondary rise begins In normal individuals this point is usually reached by 2½ to 3 minutes, in patients with pulmonary emphysema this equilibrium point may not be reached until 9 minutes or longer In some cases, the helium concentration will remain unchanged for several minutes DiSalvo and Goto have recently reported similar findings[13]

The open circuit helium washout method[22] cannot evaluate the behavior of *rapidly* ventilated lung spaces but does allow comparison of the size and distribution of gases in the *most poorly ventilated* regions of the lung.

Pneumatometric (Pressure-Volume) Methods for Measuring Lung Volumes

Two types of pneumatometric technics have been described, both based on Boyle's law relying on a measured change in volume in response to a measured change in pressure. One of these is the decompression method used by Hitchcock and his co-workers,[23] Willmon and Behnke,[49] and Dejours and Rahn[12] In this decompression method, the pressure about the body and in the lungs is raised equally above atmospheric so as to compress the gas inside the lungs and outside the body The pressures in the chamber and trachea are then released simultaneously. During the return to normal atmospheric pressure the amount of gas which flows out of the trachea is measured. This is the same volume which had been *added* by the previous pressure, the *volume change* (V_2) in response to the pressure change (P_2) The pulmonary gas volume (V_1) at atmospheric pressure (P_1) can then be calculated by Boyle's law:

$$P_1V_1 = (P_1 + P_2)(V_1 + V_2) \qquad (10)$$

Although these technics can measure the volume of gas in the lungs with reasonable accuracy, the specialized and complex equipment required make such technics impractical for clinical studies

The second pneumatometric technic is based on *voluntary* compression or decompression of lung gas and was first described in principle by Pflüger in 1882 In this method, changes in alveolar gas pressure and volume are measured while the subject makes voluntary respiratory efforts against a closed airway. This method gives values for the volume of gas in the lungs and thorax whether or not this gas is in free communication with the airway. Attempts to apply this principle for clinical or physiologic use were largely unsuccessful until Dubois and his associates applied new precise methods for measuring and recording pressure changes and developed the body plethysmograph into a useful instrument for measuring thoracic gas volume.[16]

Body Plethysmographic Method for Measurement of Functional Residual Capacity

Procedure

The subject enters and sits in a large air tight chamber with the dimensions of a tele-

nitrogen washout method are: (a) some error in the assumed 81 per cent value for the initial alveolar N_2 concentration, (b) the "C" correction factor may be slightly in error and (c) the end-expiratory gas sample may not be truly representative of the alveolar gas composition. Only the latter can produce other than very small errors In those patients with grossly uneven distribution of intrapulmonary gas, there may be a material error in the FRC volume.

As in all dilution methods, a leak of room air into the system will seriously alter the measurements Such an error is more difficult to detect when a breathing curve is not recorded Dilution methods are also limited by the ability of the subject or patient to exchange gas with all portions of the lungs Areas which are poorly ventilated may not be measurable by these methods although satisfactory measurement can usually be accomplished with longer equilibration

Open Circuit Helium Method for Measurement of Functional Residual Capacity

In 1954 Hickam, Blair, and Frayser described an open circuit helium washout method for measuring functional residual capacity[22] in which the subject first breathed 50 per cent helium and 50 per cent oxygen for 15 minutes followed by 100 per cent oxygen breathing, collection of the expired gas, and analysis of helium in the alveolar and expired air samples.

The principle is the same as that of the nitrogen open circuit method and the calculations are similar. The open circuit helium method, however, is slightly more complex than either of the other two dilution methods The only apparent advantage over the other two technics results from the greater diffusibility of helium which favors its washout rate and increases the sensitivity in assessing the size and minute ventilation of poorly ventilated regions of the functional residual capacity.

The Use of Gas Dilution Technics in Evaluating Intrapulmonary Distribution of Inspired Gas

The closed circuit helium method, the open circuit nitrogen washout method and the open circuit helium methods all are capable of assessing to some degree the adequacy of intrapulmonary distribution of gases. Although distribution of gases is discussed in greater detail in Chapter 38, it is appropriate to summarize here those aspects of inspired gas distribution which are related to the technics used in measuring lung volume

The open circuit nitrogen washout method has been widely used as a test for uneven distribution of inspired gas The simplest of the technics is the "pulmonary N_2 emptying rate" in which the nitrogen concentration of an end-expiratory gas sample is measured after the subject has breathed pure oxygen for 7 minutes. In normal individuals this 7 minute alveolar sample will contain less than 2.5 per cent nitrogen[1] If some areas of the lung are hypoventilated during normal breathing, the 7 minute alveolar N_2 concentration will be elevated

A somewhat more difficult and complex test, rarely used clinically, is the pulmonary nitrogen clearance (or washout curves) in which breath by breath measurements of alveolar nitrogen concentration are made and compared with the *theoretical* values which would be expected if the inspired O_2 were distributed evenly to all the alveoli[17] When such clearance curves are plotted on semi-log paper there may be several different clearance rates, this suggests that some regions of the lung are ventilated more rapidly than others.

The *single breath nitrogen test of uneven distribution*[7] requires the continuous recording of alveolar nitrogen concentration as the patient or subject inspires pure oxygen and then expires slowly and evenly into a spirometer or flow meter The volume of gas expired should be recorded simultaneously with the continuous record of nitrogen concentration No measurements are made on the first 750 ml. of expired gas because in some patients the portion of this volume may contain some dead space gas The change in N_2 concentration during the next 500 ml of expired gas (750 to 1,250 ml. volume) provides an index of distribution. In normal subjects the alveolar N_2 concentration should not rise more than 1.5 per cent during the expiration of this 500 ml volume. The test is simple and well adapted as a screening test.

Calculation of Thoracic Gas Volume (Functional Residual Capacity)

The equation used for calculation of thoracic gas volume (V_{TG}) is.

$$V_{TG} = \frac{970 \times \text{box calibration in ml/in}}{\lambda V_{TG} \times \text{pressure calibration in cm } H_2O/\text{in}} \quad (11)$$

970 = barometric pressure in cm H_2O − water vapor pressure,

λV_{TG} = tangent of the angle which the oscilloscope makes with the horizontal

The derivation of this equation is well detailed by Dubois and co-workers [16]

The calculation has been greatly simplified by the construction of a direct reading scale for the oscilloscope which provides the direct reading of the thoracic gas volume (FRC) from the slope of the oscilloscope trace [8]

One of the major advantages is that this technic measures all of the intrathoracic gas volume, whereas the dilution technics and other pneumatometric studies measure only the gas containing volumes which exchange gas during the period of study. This method used, in conjunction with one of the dilution technics, might be able to measure with reasonable accuracy the volume of a pulmonary cyst which does not communicate with the tracheobronchial tree

THE SIGNIFICANCE OF CHANGES IN THE FUNCTIONAL RESIDUAL CAPACITY, RESIDUAL VOLUME, AND TOTAL LUNG CAPACITY

Functional Residual Capacity

The functional residual capacity normally acts as a buffer to prevent wide fluctuations in alveolar oxygen and carbon dioxide tensions ($P_{A_{O_2}}$ and $P_{A_{CO_2}}$) during the respiratory cycle. A *decrease* in FRC is seen only in those conditions in which there is a diffuse process which reduces functioning lung tissue, such as diffuse pulmonary granulomatosis or fibrosis. The major effect of a low functional residual capacity is the occurrence of wide fluctuations in alveolar oxygen tension ($P_{A_{O_2}}$) and to a lesser degree carbon dioxide tension ($P_{A_{CO_2}}$) during the phases of respiration

An increase in FRC represents *hyperinflation* which most commonly results from *obstructive disease* whether *reversible* as in the case of airway obstruction from asthma or peribronchiolar inflammatory disease; or *irreversible* as in pulmonary emphysema, compensatory overinflation following surgical removal of lung tissue, or deformity of the thorax. Elderly individuals may at times demonstrate an elevated FRC with normal alveolar ventilation and without other evidence of pulmonary disability.

An increased FRC may act too effectively as a buffer against rapid changes in alveolar gas composition, so that responsiveness to changes in inspired gas mixtures is quite slow. With an increased FRC the thoracic cage is always larger than normal and some muscular inefficiency or mechanical disadvantage may result. With a chronically enlarged FRC, ventilation of the hyperinflated area may be poor

Some increase in FRC will result normally as a change is made from the recumbent to the upright position. This is the result of an increased expiratory reserve volume with change in position (see FIG. 3).

Residual Volume

The residual volume (RV) may be decreased in cases of diffuse disease which occludes or destroys alveoli in many regions of the lung.

We have observed progressive decreases in the residual volume in patients with diffuse pulmonary granulomatosis, and in those with diffuse pulmonary fibrosis. We have recently encountered progressive decrease in both RV and FRC in a patient with pulmonary alveolar proteinosis who is showing slow progression of his disease.

Of much greater significance is an *increase* in residual volume which means that the patient even with maximal expiratory effort cannot force his thorax and lungs back to normal size. Although an increase in residual volume may occasionally be reversible as in acute or subacute bronchitis, bronchiolitis, or bronchospastic disease, it usually is to a greater or lesser degree irreversible and represents a loss of lung elasticity or persistent bronchial obstruction.

The RV and FRC usually increase together

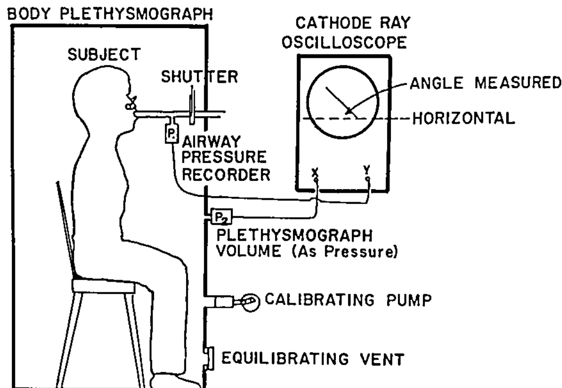


FIG 9—Schematic drawing of the body plethysmograph for measuring thoracic gas volume P_1 and P_2 are pressure transducers and their amplifying systems P_1 records the airway pressure P_2 records the volume change in the plethysmograph, having been previously calibrated so a known volume change gives a known pressure response Any change in the thoracic gas volume is reflected by an identical change in the plethysmograph volume

phone booth and a volume of approximately 600 L and breathes ambient air during the test period FIGURE 9 is a diagram showing the major features of the body plethysmograph as used for measuring thoracic gas volume V_{TG} which is, in effect, the functional residual capacity (FRC).

The volume changes in the 600 L box are determined by means of the pressure changes measured by pressure transducer P_2 and recorded on the horizontal axis of a cathode ray oscilloscope (x, FIG. 9), so that a given horizontal deflection corresponds to a known volume change.

After the temperature and humidity of the box have stabilized, the subject applies the noseclip and breathes through the mouthpiece-shutter system (FIG. 9) At the end of a normal expiration, the operator closes the solenoid-controlled shutter and the subject continues to make one or more respiratory efforts or pants. This alternately compresses and decompresses the air within his chest by the action of the chest muscles. The airway pressure is measured by pressure transducer P_1 and is recorded on the vertical axis of the oscilloscope (y, FIG. 9). At the same time changes in *thoracic gas volume* are being recorded on the horizontal axis of the oscilloscope Thus the changes in pulmonary pressure are graphed continuously against the changes in thoracic gas volume and appear as a slanting line on the oscilloscope. The slope of the line represents $\Delta P/\Delta V$ and is termed λV_{TG}.

Respiratory efforts or panting give repeated pressure volume changes which are retraced very quickly several times on the screen so that a representative slope is obtained Since each determination requires only a few seconds, repeated measurements can be made in a minute. A recent report presents a detailed description of the design of the body plethysmograph.[9]

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The Significance of Changes in the Functional Residual Capacity, Residual Volume, and Total Lung Capacity

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An increased FRC may act too effectively as a buffer against rapid changes in alveolar gas composition, so that responsiveness to changes in inspired gas mixtures is quite slow. With an increased FRC the thoracic cage is always larger than normal and some muscular inefficiency or mechanical disadvantage may result. With a chronically enlarged FRC, ventilation of the hyperinflated area may be poor.

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The RV and FRC usually increase together

although the RV may increase independently. An increase in RV is frequently accompanied by a reduction in vital capacity. In other instances, such as early pulmonary emphysema, the residual volume may increase with no change in the vital capacity In such instance, of course, a larger total lung capacity would result

An increase in residual volume, even when associated with some reduction in vital capacity may not be associated with serious pulmonary disability since the full vital capacity is rarely needed to achieve adequate alveolar ventilation even with moderate exercise (see Fig. 4).

In clinical usage, the residual volume is most often evaluated in relation to the total lung capacity and expressed as the RV TLC ratio An increase in this ratio does not necessarily indicate hyperinflation since an increased ratio may result not only from an increase in residual volume but also from a reduction in total lung capacity with no change in the residual volume This may occur in such conditions as pulmonary congestion or fibrosis or even with tight strapping of the chest Although the RV TLC ratio may serve as a helpful index, it should be interpreted only in relation to the absolute value for the residual volume Although some early studies have concluded that an RV TLC ratio greater than 35 per cent is strongly suggestive of hyperinflation[1] or impaired alveolar ventilation,[25] other investigators, studying groups of older people in good health, have recently found mean values for the RV/TLC ratio of 35 per cent,[3] 41 per cent (males) and 42 per cent (females),[18] and 39 per cent (males) and 41 per cent (females).[41] Individual RV/TLC ratios in these series were as high as 50 per cent.

Normal Values for Lung Volumes

Because of the simplicity and rapidity with which vital capacity can be measured there are abundant reports with tables of normal standards and formulae for prediction. Some of these prediction formulae are listed in Table 2

Since measurement of functional residual capacity, residual volume and total lung capacity require more complex techniques, the number of reports and of subjects studied is much smaller. Table 3 presents a survey of the various compartments of the lung volume in relation to age. The older studies of Kaltreider, Fray and Hyde[27] are presented for both an older and younger age group along with the figures of Robinson[46] Along with these older studies are the newer figures of Greifenstein and associates[18] for an older age group and those of Needham, Rogan, and McDonald[41] for a wide age span

It is well established that the vital capacity correlates directly with height and inversely with age Table 3 clearly demonstrates the fall in vital capacity with age The RV appears to remain constant up to age 60 in males and to age 50 in females, after which it appears to increase slightly The FRC shows even less variation with age In both males and females, the RV TLC ratio shows a gradual but consistent increase with advancing age. The increase in this RV TLC ratio is a reflection of both the slight increase in RV and the larger decrease in the vital capacity

Further study of Table 3 shows that the FRC, RV, and RV TLC ratios are all much lower in the series of Kaltreider, Fray and Hyde's series than in any of the other groups. These differences are so large and so consistent that one must conclude that the technical differences between the oxygen dilution technique and the other procedures (helium dilution and nitrogen washout) will not permit comparison of the data Such technical differences may well explain the disagreements about the RV/TLC ratios above 35 per cent It would appear that by Kaltreider's technic both the RV and FRC are much lower than they are in any of the other studies.

Needham, Rogan, and McDonald[41] have further shown that the RV/TLC ratio correlates just as highly with age as does the vital capacity Their regression equations for the RV/TLC ratio may well prove useful as prediction formulae.

Males—20 to 70 years

$$RV/TLC \times 100, \% = 0.43 \times \text{Age in years} + 16.3$$

Females—20-70 years

$$RV/TLC \times 100, \% = 0.33 \times \text{Age in years} + 22.7$$

TABLE 3.—*Normal Lung Volumes*

Mean Values For	Kaltreider, Fray and Hyde[27] N = 50	Needham, Rogan and McDonald[illegible] N = 27	N = 23	N = 22	N = 20	N = 10	Kaltreider, Fray and Hyde[27] N = 50	Robinson[44] N = 29	Griefenstein et al[18] N = 11
Males									
ge (yr)	22.9	25 2	35	44.9	54.3	64.2	48.2	59 8	61.5
leight (cm.)	176 2	175 8	173.8	172.0	166.3	171 6	170.5	174 0	169
Veight (Kg)	72 5	70 5	70	68.7	65	68 3	70.8	68.3	65 9
nspiratory capacity (L)	3 79	3 29	3 08	2 89	2 45	2 41	3.37	3.26	2.61
Expiratory reserve volume (L.)	0.98	1.47	1 43	1 14	0.98	0 86	0.69	0.72	1.01
Vital capacity (L)	4 77	4.76	4 51	4 03	3 43	3.27	4.06	3.97	3 48
Functional residual capacity (L.)	2 18	3 21	3.55	3.30	3 16	3 56	2 00	2 49	3 44
Residual volume (L)	1.19	1 75	2 11	2 17	2 20	2.70	1 31	1 79	2.43
Total lung capacity (L.)	5 97	6.50	6 63	6.19	5 61	5 97	5.37	5 92	5.92
RV/TLC × 100 (%)	19.8	26 6	32 0	34 8	39 0	44 9	24.5	30.2	40 9
Females									
		N = 18	N = 13	N = 11	N = 16	N = 8	Greifenstein et al[18] N = 14		
Age (yr)	23 1	24.4	34 3	46 2	54 1	64 6	60 9		
Height (cm)	163.4	161 3	161 0	160 3	158	158 5	157		
Weight (Kg)	57 2	57 9	55 1	63 8	56 5	63 0	66.8		
Inspiratory capacity (L)	2.42	2 22	2 21	2 07	1 83	1.69	1 96		
Expiratory reserve volume (L)	0 73	0.90	0.95	0 57	0.61	0.49	0.44		
Vital capacity (L)	3 15	3 12	3 16	2 64	2 44	2 18	2.40		
Functional residual capacity (L)	1 82	2 34	2 44	2 07	2 29	2 34	2 22		
Residual volume (L)	1.10	1 46	1.52	1 50	1 68	1.82	1 78		
Total lung capacity (L)	4 24	4 56	4 63	4 14	4 12	4 00	4 14		
RV/TLC × 100 (%)	25 9	31 9	32.7	35.6	40.6	45.1	41.9		

SUMMARY

The vital capacity is the most easily performed and most widely used test of pulmonary function. Its value is greatly enhanced by the addition of timed volume measurements and flow rates Although increasingly valid prediction formulae have been devised, deviations from "normal values" must still be quite large to be of diagnostic significance. A truly reduced vital capacity, however, is good evidence of the presence of abnormal cardiopulmonary function

The technics for the measurement of functional residual capacity and residual volume have been sufficiently simplified in recent years to permit their widespread use. The several technics currently in use all give accurate and reproducible measurements. Although these tests are not as valuable as vital capacity measurements, they provide a useful adjunct in the assessment of pulmonary function.

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Mechanics of Breathing

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THE disability of pulmonary disease is ordinarily proportional to dyspnea, which is imperfectly, but still most nearly, related to respiratory effort.[1] The effort required to achieve a given alveolar ventilation is determined by the mechanical properties of the lung parenchyma, thoracic cage and airways as well as by the distribution of these properties within the lung. Studies of the basic mechanics of respiratory activity are of major importance not only for the purpose of elucidating the fundamental nature of pulmonary disease but also as a basis for guiding rational therapy of respiratory insufficiency.

In the following presentation, only principles are exhibited and no attempt will be made to present the details of methods, for which the reader should consult specific reference sources.

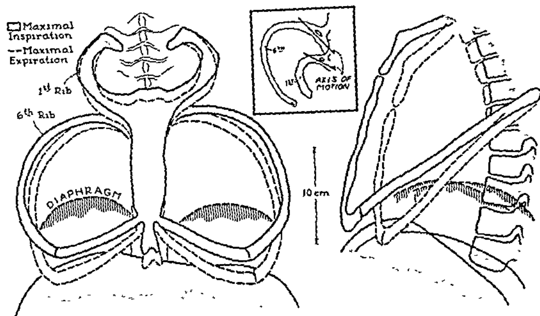
ANATOMIC CONSIDERATIONS

The pleural surfaces of the lung are intimately applied to the inner pleural surfaces of the thoracic cavity and held there by atmospheric pressure, less recoil pressures of the lung and thorax. Only a thin film of lymph is interposed between these two surfaces to form a potential pleural space, and because of the firm and intimate contact, the shape and volume of the lung must conform to that of its thoracic container. Thus, before discussing specific forces involved with ventilation, it seems desirable to consider the degree of freedom with which the thoracic cavity and its contents may change in volume and shape.

Thoracic Motion

FIGURE 1 shows the relative positioning of the rib cage, diaphragm and thoracic vertebral column at full inspiration and full expiration. The rib cage is hinged posteriorly to transverse processes and bodies of thoracic vertebrae and attached anteriorly to manubrium and sternum through semiflexible cartilage.[2] During inspiration, the rib cage rotates upward on these costovertebral hinges to place the rib planes more nearly perpendicular to the spine. The manubrium and sternum rise and the anteroposterior diameter of the chest increases. The angulation of the axis of the costovertebral hinges with respect to the sagittal body plane (FIG. 1) also causes an anterolateral flaring of the ribs and an increase of the transverse diameter of the chest which is most pronounced in the lower and mid thoracic regions. During inspiration, the surface area of the diaphragm decreases by intrinsic muscular contraction, while the cross-sectional area of the rib cage increases. As a consequence of both events, the two leaves of the diaphragm are pulled down and their curvature reduced. The net result of all of these thoracic movements is an expansion of thoracic volume by extensions of all major chest diameters. As indicated in FIGURE 1, extension and flexions of the spine further increase the range of thoracic motions. Normal quantitative changes in thoracic dimensions are given in TABLE 1.

Raising the rib cage beyond a point at which the rib planes are perpendicular to the spine can produce no further increase in thoracic volume. Also, descent of the diaphragm by intrinsic muscular contraction is limited to that point at which its surface becomes flat. These two factors provide a theoretical limit to maximal volume of the thorax, but in normal subjects this limit is not approached even during a



first and sixth ribs.

maximal inspiration. In athletes or in subjects who spend most of their lives at very high altitudes, the ribs may be more perpendicular to the spine during deep inspiration and these subjects may achieve greater maximal thoracic volumes than average subjects.[3,4] In some patients with advanced pulmonary emphysema, the theoretical maximum must be approached at full inspiration when ribs are almost perpendicular to the spine and the diaphragm is flattened

Structural properties within the chest which tend to limit the thorax to a volume less than the theoretical maximum are lung distensibility, distensibility of the enveloping skin and fascia and the flexibility of costovertebral joints, chondral parts of the ribs, and the costosternal and steromanubrial joints The extensibility of the mediastinum and the central portions of the diaphragm may also serve to limit chest expansion It has been suggested that inspiratory muscle effort in normal subjects is reduced by reflex inhibition of inspiratory muscles as maximal inspiration is approached. This inhibition serves to prevent harmful overdistention of the lung [5]

TABLE 1 — *Quantitative Changes in Thoracic Dimensions**

	Vital Capacity	Quiet Breathing
Cephalocaudal chest displacement	0–5 cm	0
Chest circumference (midthorax)	4–12 cm	0 5–2 0 cm
Diaphragm displacement (with respect to the spine)	4–10 cm	1.5–2 0 cm
Diaphragm displacement (with respect to its thoracic insertion)	7–14 cm	1 5–2 0 cm

* From the data of Wade [2]

Asymmetry of Thoracic Movement in Relation to Distribution of Inspired Air and Blood Flow

The thorax does not expand uniformly in all directions The upper thorax expands least and is limited for the most part to anterior and caudal displacement, whereas the lower thorax expands anteriorly, laterally, and caudally. Thus, in normal subjects, the upper lobes receive a smaller portion of the inspired air with respect to alveolar volume than do the lower lobes [6] Mediastinal and paravertebral surfaces of the thoracic cavity remain relatively fixed,

and lung units opposed to these surfaces probably expand less well in response to a given distending pressure than do those units opposed to the anterior or diaphragmatic thoracic walls. Asymmetrical chest expansion may alter not only the intrapulmonary distribution of inspired air but also the intrapulmonary distribution of blood flow Thus, in spite of the relatively poor ventilation of upper lobes with respect to lung volume, these lobes are overventilated with respect to blood flow[7] The preferential distribution of blood through the lower lobes may result not only from a greater distention of blood vessels by hydrostatic forces in dependent areas but also by greater tidal distention of the arterial and venous beds of the lower lobes associated with the greater tidal lung expansion[8, 9]

Muscles of Respiration

FIGURE 2 shows the general function and segmental innervations of some of the important muscles of respiration. During quiet breathing only inspiratory muscles are activ expiration being a passive result of thoracic an lung recoil. The external intercostals, di phragm and possibly the scaleni provide th force for quiet tidal inspirations. According t Campbell, it is not until levels of ventilatio approaching 40 to 60 L. per minute are ap proached that accessory muscles of inspiratio and expiration become active in normal exer cising subjects[5] For a more extensive analysi of the muscles of respiration, the reader i referred to the excellent monograph by Camp bell.[5]

FORCES OF RESPIRATION

Forces related to ventilation are measure as pressure and may be described in terms o static and dynamic components. The stati components (recoil) are independent of th motion of the lungs and thorax Dynamic force of frictional and inertial resistance, on th other hand, are dependent upon rate and direction of ventilatory movements

CRANIAL: 11, 12
CERVICAL: 1, 2, 3, 4, 5, 6, 7, 8
THORACIC: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
LUMBAR: 1, 2, 3

INSPIRATION: St M; Diaphragm; Scaleni; Pectoralis Maj & Min.; Lat Dorsi; Serratus P S; External Intercostals; Levator Costarum

EXPIRATION: Internal Intercostals; Subcostals; Sterno-costals; Rectus Abdominis; Obliquus Abdominis; Transversus Abdominis; Serratus P I

FIG 2—Segmental innervation of respiratory muscles Some of the muscles in the diagram may have dual respiratory function which has not been indicated. Thus, the latissimus dorsi may be an expiratory muscle under certain circumstances, and it is generally accepted that the intercartilaginous portion of the internal intercostals aid inspiration The sacrospinalis has not been included in this diagram because of its complex nature; this group of muscles probably supplies both inspiratory and expiratory force. St M, sternocleidomastoid muscle; Serratus P S, serratus posterior-superior; Serratus P I, serratus posterior inferior.

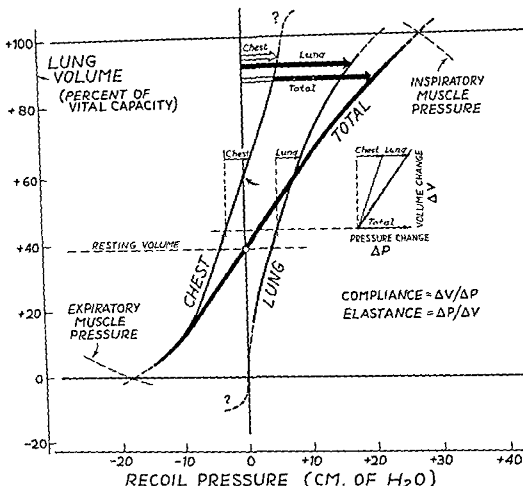


Fig 3 —*Typical static pressure-volume diagram* Positive recoil pressure on the horizontal axis also corresponds to negative intrapleural pressure for the lungs, and positive intrapleural pressure for the chest (thoraco-abdominal apparatus) In practice, chest recoil is obtained as difference between lung and total recoil. Recoils are added algebraically as shown by the arrows at the top. Changes in recoil are added as shown by the compliance-elastance diagram inserted to the right The curves shown have typical shapes; extrapolations are dotted As discussed in the text, static effort of respiration is shown by slope (compliance or elastance) and standard lung volumes are shown by intersections of the total curve with zero pressure and with maximal muscle pressures The effects that variations in slope, zero intercept, and exact shape of individual recoil curves may have on ventilatory volumes and pressures can be derived by making appropriate alterations of the figure

Static Forces

Muscular effort* provides the prime driving force of respiration and is alternately hindered and aided by chest and lung recoil Recoil, which is measured during apnea, arises from elasticity, surface tension, and weight, and varies with body position and degree of inflation of the breathing apparatus. The variation of recoil with lung volume may be shown by static pressure volume diagrams,[10] such as in Figure 3. Lung and chest recoil vary both in magnitude and direction at different lung volumes and have different intercepts or positions of zero recoil The pull holding chest and lungs together is manifest as negative intrapleural pressure, and if this pressure is made atmospheric by opening the chest, the lungs will retract and the chest will expand to respective

and lung units opposed to these surfaces probably expand less well in response to a given distending pressure than do those units opposed to the *anterior or diaphragmatic thoracic walls* Asymmetrical chest expansion may alter not only the intrapulmonary distribution of inspired air but also the intrapulmonary distribution of blood flow. Thus, in spite of the relatively poor ventilation of upper lobes with respect to lung volume, these lobes are overventilated with respect to blood flow[7] The preferential distribution of blood through the lower lobes may result not only from a greater distention of blood vessels by hydrostatic forces in dependent areas but also by greater tidal distention of the arterial and venous beds of the lower lobes associated with the greater tidal lung expansion[8, 9]

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CRANIAL | CERVICAL | THORACIC | LUMBAR
11 12 | 1 2 3 4 5 6 7 8 | 1 2 3 4 5 6 7 8 9 10 11 12 | 1 2 3
INSPIRATION
St M
Diaphragm
Scaleni
Pectoralis Maj & Min.
Lat Dorsi
Serratus P S
External Intercostals
Levator Costarum
EXPIRATION
Internal Intercostals
Subcostals
Sterno-costals
Rectus Abdominis
Obliquus Abdominis
Transversus Abdominis
Serratus P I

FIG 2—Segmental innervation of respiratory muscles Some of the muscles in the dia-

remain unaltered. Thus, interpretation of changes in lung or chest compliance in terms of changes in supporting tissues must be made with considerable caution. This should become even more apparent from the discussion to follow about surface tension as a factor in determining lung recoil.

Surface tension is an important source of static recoil force in the lungs because of the small dimensions of individual surface enclosed volumes. In contrast to elastic wall tension, which increases with stretch and thus decreases toward zero at small volumes, simple wall surface tension at the interface between air and wet wall is essentially constant. According to Laplace's law (recoil pressure ∝ wall tension/radius), the recoil effects of *constant* wall surface tension increase with decreasing volumes. Thus, as dimensions of small air spaces decrease, the increasing effect of surface tension may cause sudden collapse. If small airways collapse, air may be trapped within distal units. Clements and co-workers[14] have stressed the importance of a *variable* surface tension observed in lung extracts but, for present purposes, such behavior can be considered as a combination of simple surface tension plus elasticity. During expansion any small area of collapse tends to remain occluded until the expansile force reaches a critical level of pressure at which the unit suddenly opens. Under these circumstances, the critical opening pressure is always higher and may be considerably higher than critical closing pressure. Consequently, the most obvious result of surface tension on static pressure-volume behavior,[15] as illustrated in FIGURE 4, is to cause *hysteresis*, that is, behavior of the system does not follow *the same* path when moving in one direction as when moving in the opposite direction, so that a static P-V loop is formed. Static hysteresis is small during ordinary tidal volume exchange, but increases with greater volume exchange. When hysteresis is marked, compliance varies greatly throughout the respiratory cycle. FIGURE 4 also shows that static hysteresis depends largely on the presence of air-fluid interfaces in the lungs, since collapsed lungs inflate readily in a saline medium in which the air-fluid interface has been effectively eliminated. Once the lungs are completely inflated, the static P-V curve during deflation of air-filled lungs is similar to that of saline-filled lungs.

Weight contributes to static recoil primarily by shifting the entire chest recoil curve; hence, compliance does not reflect changes of weight load directly. However, changes in the mechanical properties of the lungs may result from secondary effects of this *shift*, e.g., in the recumbent position, functional residual capacity decreases, thus increasing the likelihood of occluding lung volume units. Also, redistribution of fluid and blood into the lungs makes the dependent portions more congested. Ordinary weight forces increase chest recoil about 5 to 10 cm. H_2O in recumbency. This increase in recoil pressure corresponds to a mid-range volume decrease of 0.5 to 1.0 L. in an average adult.

Dynamic Forces

During respiration, muscular effort is necessary to overcome frictional and inertial resistance, commonly called nonelastic resistance. The most important dynamic force is frictional resistance to air flow. Other forces, namely, frictional resistance to tissue flow and inertial reaction to acceleration, are small and usually included in the measurement of frictional resistance to air flow.

The ratio of frictional pressure drop to rate of air flow is a specific resistance ($\Delta P/\dot{V}$). Since specific resistance (R) may vary during respiration, it frequently is expressed at a standard flow rate, such as 0.5 L. per second in the mid-volume range. Under certain circumstances the relation of frictional pressure drop to rate of flow is best shown as the reciprocal of R or conductance ($\dot{V}/\Delta P$). Conductance is useful for comparison to lung volume functions because, for the most part, it varies directly with the number and size of functioning airways and related lung volume units. In normal subjects, airway dimensions vary with lung inflation in such a way that, when laminar flow predominates, conductance in L. per second/cm. H_2O remains approximately equal to one-fifth of the lung volume in liters.[16]

The magnitude of the pressure drop associated with air flow depends on system di-

positions of zero recoil Chest and lung recoil act in opposite directions in the mid-volume range and at some point balance one another, this position of equilibrium is called the resting midposition The functional residual capacity is equal to the volume of air in the lungs at the resting midposition only when sufficient time exists between breaths for static equilibrium to be reached and when the muscles are relaxed at the end of expiration

If data on maximal effective pressure available from muscle effort are included, the *static* P-V diagram contains all the factors determining static lung volumes Total capacity and residual volume are achieved when maximal pressure from muscle effort equals total recoil. FIGURE 3 shows that the pressure from muscle effort decreases rapidly at extremes of volume. Probably, the respiratory muscles are relatively ineffective at those extremes and the pressure they produce may bear little relation to the total amount of muscle effort

The slope of a recoil curve reflects distensibility and is called compliance (FIG. 3) This measure is volume change divided by the associated change in recoil pressure ($\Delta V/\Delta P$, L./cm H_2O; its reciprocal ($\Delta P/\Delta V$) reflects stiffness and is called elastance. When structural units under consideration are in parallel (e.g , adjacent alveoli, as shown in FIGURE 10), their compliances are added to obtain total compliance. When structural units are in series (e g , the lungs and thorax), their elastances are added to give total elastance.

Typical compliance values for normal adults are about 0 2 L./cm H_2O for either the lungs or chest alone and 0.1 L., cm. H_2O for the total apparatus. The equivalent elastances are 5 and 10 cm. H_2O L., respectively Thus, a normal tidal inflation of 600 ml. requires about 6 cm. H_2O pressure developed by muscle effort to overcome total change in recoil About 3 cm. H_2O of this pressure is manifest as a change in negative intrapleural pressure overcoming increased lung recoil, while the remainder acts within the chest to overcome increased chest recoil Among different individuals, lung compliance varies directly with lung size, so that about the same pressure change is required for a normal tidal volume in adults and infants (TABLE 2)

Elastic behavior of the respiratory system is complex for a number of reasons The stress-strain behavior of natural elastomers *such as* connective tissue is generally nonlinear and may exhibit reversible "creep" or flow.[12] The component tissue elements in the lung exhibit different stress-strain behavior, e g , the elastance of elastic and collagenous connective tissues differ by about a hundred-fold,[13] and at a given lung volume one component may be flaccid or stretched to a different extent than another component. Furthermore, the relationship between the lung volume, the distending pressure, and the strain in the septal tissues is not simple and direct Tension in the wall of a cylinder or spherical structure is proportional to the product of distending pressure and radius of wall curvature (Laplace's law); therefore, a small spherical unit will be more resistant to pressure distention or exhibit a greater recoil pressure than a larger unit having the same wall tissue composition and the same wall thickness. Also, a greater pressure may be required to change the shape and volume of an elastic structure than to change volume alone, therefore, changes in the way in which the thorax is expanded may alter the static pressure-volume relationships of both thorax and lungs even though the supporting tissues per se

TABLE 2 —*Summary of Mechanical Properties in Normal Subjects**

Compliance of lungs, L /cm H_2O
- children and adults (0 055 ± 0 01)FRC†
- children and adults (0 036 ± 0 01)VC‡

Compliance of thorax, L /cm H_2O, essentially the same as for the lungs

Conductance, L /sec./cm H_2O

$$\text{Total conductance} = \frac{1}{\text{total nonelastic resistance}}$$

- infants 0.44 FRC
- children 0 15 FRC (range = 0 090–0 174)
- adults 0 14 FRC (range = 0 092–0 286)

$$\text{Airway conductance} = \frac{1}{\text{airway resistance}}$$

- children 0.17 FRC (range = 0 14–0 20)
- adults 0 24 FRC (range = 0 19–0 36)

Tissue viscous resistance—15–20 per cent of total

* Data from multiple sources included in bibliography.

† FRC = functional residual capacity

‡ VC = vital capacity.

Laminar resistance depends largely on viscosity, while turbulent resistance depends essentially on density. This is illustrated by the difference between pressure drop curves for helium and for air. Helium has about the same viscosity as air but only about one-seventh the density. The relation of pressure drop to flow rate for a *fixed* system thus can be expressed in a grossly simplified manner as:

$$\textit{Pressure drop} = k_L\dot{V} + k_T\dot{V}^2,$$

where k_L and k_T are theoretical laminar and turbulent resistances, respectively, which can be calculated for any tubular system with fixed dimensions through which any gas of known density and viscosity is flowing.[13] This simplified equation for a rigid tubular system does not show the exact effect of a change from laminar to turbulent flow pattern, such as is illustrated by the curves for air in FIGURE 5. As steady flow through straight tubes is increased, change from laminar to turbulent flow begins when a flow parameter called the Reynolds number* reaches a value of 2,100, and change is complete after a short transition range. When flow is changing rapidly or there are irregularities of the flow channel, turbulance may begin at other Reynolds numbers. A Reynolds number of 2,100 occurs in a 2 cm. diameter trachea at a respiratory air flow of about 50 L. per minute, and at higher respiratory flow rates in smaller airways. The exact flow rate at which turbulent flow begins during alternating respiratory flow through branching airways is not known, but this transition must occur during forced respiration.

Curves for the relationship between rate of flow and pressure drop in fixed systems correspond only in an empirical way to curves observed during respiration in an elastic system of conducting airways where airway dimensions are constantly changing. The *two types of* curves are related in a manner which is easily understood. There will be a thoretical pressure drop curve for each set of instantaneous *airway* dimensions. During a tidal breath, the relations of pressure drop to flow will fall, first on one curve and then the next, so that the functional curve for the elastic airways will lie *across* the theoretical curves for fixed systems.

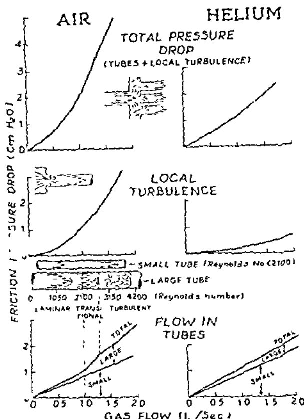


FIG. 5.—Frictional pressure drop in an arbitrary fixed system. Calculated total pressure drop consists of components depending on laminar flow in tubes, turbulent flow in tubes, and local turbulence or disturbances in momentum. These components vary differently with respect to flow rate, system dimensions, and gas properties. (The properties of helium with respect to air are: viscosity, 1.08, density, 0.16.) In steady flow, the transition from laminar to turbulent flow in tubes begins at a Reynolds number of about 2,100 and proceeds approximately as illustrated.

Average specific resistance (R) in normal adults is about 2 cm. of H_2O per L. per second so that a flow rate of 0.5 L. per second requires *about 1.0 cm.* of pressure. Since R varies inversely with lung size, smaller individuals exhibit a higher value[16, 19, 20] (TABLE 2).

In summary, nonelastic resistance depends on the rate of air flow and thus can be estimated as a specific resistance (R), which varies essentially as follows:

1. During respiration, R decreases as the lungs and airways expand.

* The Reynolds number is a dimensionless ratio of the product of diameter, velocity, and density to viscosity.

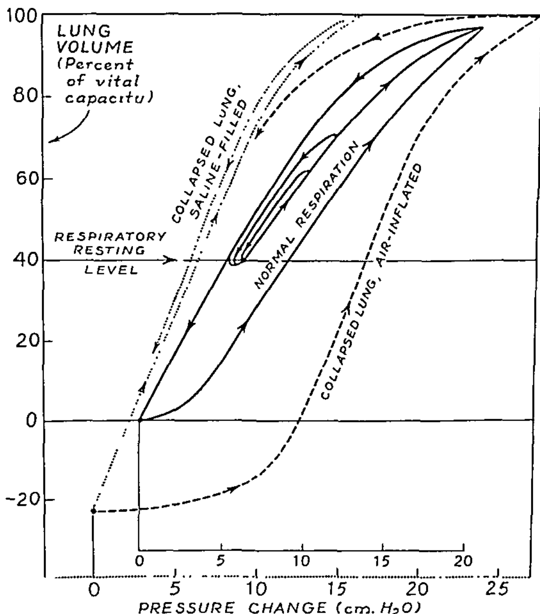


FIG 4 —*Surface tension and static pressure-volume hysteresis in the lungs* The solid lines describe typical hysteresis of static P-V curves for normal human subjects breathing at different tidal volumes As tidal volume increases, the hysteresis loop widens Hysteresis is most

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mensions, flow rate, and physical properties of the gas, according to the equations of fluid dynamics.[17] Pressure drop at any rate of flow increases directly with the length and with the fourth or fifth power of decrease in diameter of airways, depending on whether flow is laminar or *turbulent*. When system dimensions are fixed, pressure drop increases with flow rate, as illustrated for an arbitrary flow channel in FIGURE 5. This figure also demonstrates the basis for simplifying a complex flow situation by considering over-all frictional pressure loss as composed of a linear portion dependent on the first power of flow rate and a parabolic portion dependent on the square of flow rate. The linear portion arises mostly from laminar flow in tubes, and is called laminar resistance; the parabolic portion depends on local turbulence (changes in momentum) and on turbulent flow in tubes, and is called turbulent resistance.

Laminar resistance depends largely on viscosity, while turbulent resistance depends essentially on density. This is illustrated by the difference between pressure drop curves for helium and for air. Helium has about the same viscosity as air *but only about one-seventh* the density. The relation of pressure drop to flow rate for a *fixed* system thus can be expressed in a grossly simplified manner as

$$\textit{Pressure drop} = k_L \dot{V} + k_T \dot{V}^2,$$

where k_L and k_T are theoretical laminar and turbulent resistances, respectively, which can be calculated for any tubular system with fixed dimensions through which any gas of known density and viscosity is flowing.[15] This simplified equation for a rigid tubular system does not show the exact effect of a change from laminar to turbulent flow pattern, such as is illustrated by the curves for air in FIGURE 5. As steady flow through straight tubes is increased, change from laminar to turbulent flow begins when a flow parameter called the Reynolds number* reaches a value of 2,100, and change is complete after a short transition range. When flow is changing rapidly or there are irregularities of the flow channel, turbulance may begin at other Reynolds numbers. A Reynolds number of 2,100 occurs in a 2 cm. diameter trachea at a respiratory air flow of about 50 L. per minute, and at higher respiratory flow rates in smaller airways. The exact flow rate at which turbulent flow begins during alternating respiratory flow through branching airways is not known, but this transition must occur during forced respiration.

Curves for the relationship between rate of flow and pressure drop in fixed systems correspond *only in an empirical way to curves* observed during respiration in an elastic system of conducting airways where airway dimensions are constantly changing. The two types of curves are related in a manner which is easily understood. There will be a thoretical pressure drop curve for each set of instantaneous airway dimensions. During a tidal breath, the relations of pressure drop to flow will fall, first

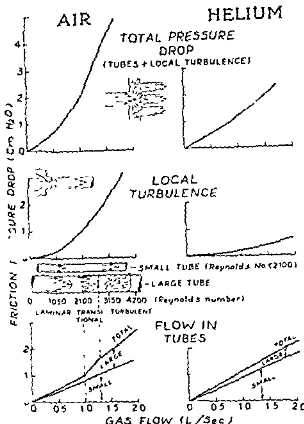


FIG. 5.—Frictional pressure drop in an arbitrary fixed system. Calculated total pressure drop consists of components depending on laminar flow in tubes, turbulent flow in tubes, and local turbulence or disturbances in momentum. These components vary differently with respect to flow rate, system dimensions, and gas properties. (The properties of helium with respect to air are: viscosity, 1.08; density, 0.16.) In *steady* flow, the transition from laminar to turbulent flow in tubes begins at a Reynolds number of about 2,100 and proceeds approximately as illustrated.

on one curve and then the next, so that the functional curve for the elastic airways will lie *across* the theoretical curves for fixed systems.

Average specific resistance (R) in normal adults is about 2 cm. of H_2O per L. per second so that a flow rate of 0.5 L. per second requires about 1.0 cm. of pressure. Since R varies inversely with lung size, smaller individuals exhibit a higher value[16, 19, 20] (TABLE 2).

In summary, nonelastic resistance depends on the rate of air flow and thus can be estimated as a specific resistance (R), which varies essentially as follows:

1. During respiration, R decreases as the

* The Reynolds number is a dimensionless ratio of the product of diameter, velocity, and density to viscosity.

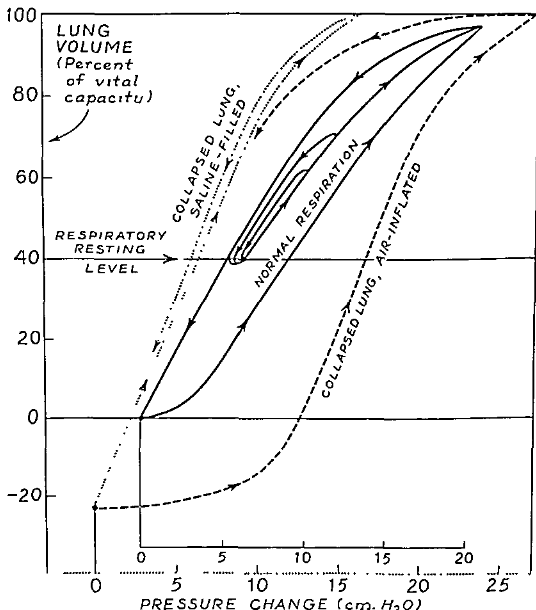


FIG 4 —*Surface tension and static pressure-volume hysteresis in the lungs* The solid lines describe typical hysteresis of static P-V curves for normal human subjects breathing at different tidal volumes As tidal volume increases, the hysteresis loop widens Hysteresis is most

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FORCES OF RESPIRATION

Forces Measurable as Pressure

- P_O – Airway outlet pressure
- P_A – Alveolar pressure
- P_P – Intrapleural pressure
- P_B – Effective body pressure

Individual Derived Forces

- P_{EL} – Lung recoil
- P_{ETh} – Thoracic recoil
- P_{Vair} – Airflow resistance
- P_{VL} – Lung tissue resistance
- P_{VTh} – Thoracic tissue resistance
- P_M – Effective muscle force

VOLUNTARY BREATHING

(where $P_O - P_B = O$)

Forces Acting on Lung | **Forces Acting on Thoracic Apparatus**

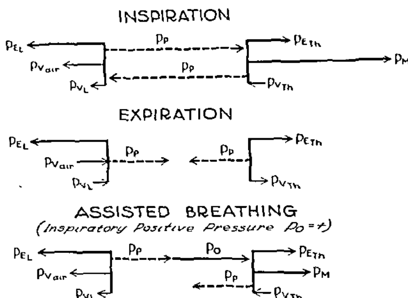


FIG 6 —*Forces of respiration* Each component force acting upon the lung or thorax at any instant is represented by an arrow, the direction of which indicates the direction of the force and the length of which indicates its magnitude Static forces are represented by heavy continuous arrows, dynamic forces by thin continuous arrows, and intrapleural pressure is a dashed arrow The algebraic sum of muscle and static forces initiate and sustain respiratory movements Frictional forces are always directed to oppose motion, while inertial forces are directed to oppose acceleration In practical measurements, inertial force is unavoidably included in estimates of frictional resistance When muscle and static forces acting in one d...

... amount of muscle force so that transpulmonary pressure remains the same The same *decrease in transthoracic* pressure occurs when assistance is given by applying a negative body pressure

proximate a static pressure-volume curve by extending a straight line through the points of apparent zero air and tissue flow.* The small diagrams (upper right) show how decreased compliance slants the static line more to the right, while increased resistance or increased flow widens the loop

Each point on a dynamic P-V loop represents the algebraic sum of the forces active in the

* Such a schematic method of estimating lung recoil and resistance results in any static curvature or hysteresis erroneously appearing as resistance

2. When volume units and their airways are effectively occluded in some portions of the lung, *R increases as ventilated volume decreases*

3. When airways are generally narrowed, R increases since airway conductance (1/R) varies in a direct linear fashion with the fourth or fifth power of airway diameter.

4. *During expiration, particularly forced expiration*, airways tend to collapse so that R increases, and it may increase to a point where it becomes virtually meaningless, i e, when a point is reached when flow cannot be increased by additional effort[21] (FIG. 16)

5. When breathing helium, only that portion of resistance which results from turbulence *during air breathing is decreased*

Tissue Frictional Resistance

Friction also exists in moving tissues According to Marshall and DuBois,[22, 23] lung tissue frictional resistance is only about one-fifth of total nonelastic resistance in normal subjects and in the few disease states in which it has been estimated. Larger estimates of tissue friction by less direct methods may have included static hysteresis due to surface tension. Extrapulmonary tissue resistance has not been separated clearly from static hysteresis and residual muscle activity, but judging from intraesophageal pressure-volume curves in *paralyzed* subjects, static hysteresis plus nonelastic resistance in the extrapulmonary tissues is of the same order of magnitude as normal intrapulmonary nonelastic resistance.

Inertia

When the rate of flow is changing, dynamic forces which depend on mass times acceleration are developed, but are probably small except during rapid changes such as occur during cough or performance of an MBC Inertial forces of air flow have been estimated to vary from about 0.02 cm. of H_2O during quiet breathing to perhaps 2 cm. during maximal expiratory flow acceleration of 200 L./sec.^{2}(see ref. 24). Inertial forces in lung tissue are even less. Extrapulmonary *inertial* forces have never been clearly demonstrated, but are perhaps about the same order of magnitude as inertial reaction of air.[25]

SUMMATION OF FORCES DURING RESPIRATION

Any over-all consideration of forces of respiration embodies the basic principle of mechanics that every force is opposed by an equal force *This can be conveniently described* for the pulmonary apparatus in a force diagram (FIG 6) For completeness, the pressure differences which can be measured in the breathing apparatus are listed below in relation to the sum of static and dynamic forces to which they are equivalent.

Transpulmonary pressure difference,

$$P_o + P_p = P_{\dot{V}_{air}} + P_{\dot{V}_L} + P_{EL}$$

Trans-airway pressure difference,

$$P_o + P_A = P_{\dot{V}_{air}}$$

Trans lung wall pressure difference,

$$P_A + P_p = P_{\dot{V}_L} + P_{EL}$$

Transthoracic pressure difference,

$$P_p + P_B = P_{VTh} + P_{ETh} + P_M$$

Trans total pressure difference,

$$P_o + P_B = P_{\dot{V}_{air}} + P_{\dot{V}_L} + P_{EL} + P_{VTh} + P_{ETh} + P_M$$

To use these formulae, an algebraic sign corresponding by some arbitrary convention to direction of action must be given to each gauge pressure and force P_o and P_p, which are airway outlet pressure and effective body pressure on the surface of the chest, abdominal wall, and diaphragm, are zero except under unusual circumstances, such as during assisted respiration.

The continuous interplay of the above forces throughout respiration can be shown best by *dynamic* pressure-volume diagrams, such as that analyzed schematically in FIGURE 7. In the upper left diagram, lung volume is plotted against intrapleural pressure. If respiration were infinitely slow, pressure would fall along a segment of the *static* lung recoil curve (FIG. 3) but during active respiration, because of nonelastic resistance, the relationship between intrapleural pressure and lung volume is a loop which intersects the static curve at points of zero resistance It is common practice to ap-

pressure-volume loop, having to be inferred from other data obtained on paralyzed or "completely relaxed" subjects; however, for completeness, a hypothetical P-V loop for the chest wall has been included as a dashed loop and the individual chest forces (not including muscle force) have been represented as dashed lines. The direction of the arrows indicates the direction of the forces The net muscle force at any instant during respiration is that which opposes the algebraic sum of the individual chest and lung forces. The term net muscle force is used to indicate that both inspiratory and expiratory muscle forces may at times act simultaneously. During normal inspiration the net inspiratory muscle force as shown probably represents total force, since there is no evidence of significant restraining expiratory muscle effort During passive expiration there exists a certain amount of residual inspiratory muscle force which must be overcome by forces of chest and lung recoil. This is indicated in FIGURE 7 by the fact that the algebraic sum of the individual chest and lung forces during a passive expiration is not zero At least part of this muscle force appears to be an active restraining muscle effort,[5] but it is not clear how much represents some kind of inability of active muscles to relax instantaneously. During a forced expiration, active expiratory muscle effort, which increases expiratory flow, is reflected as a shift of the expiratory intrapleural pressure curve toward a more positive pressure Additional shift may occur as a result of diminished restraining inspiratory force Thus, total expiratory force is the net force shown in the diagram, plus any amount needed to overcome persisting inspiratory force.

The remainder of FIGURE 7 deals with the mechanical work and will be discussed in the next section

Energy and Work of Breathing

The energy requirements of respiratory muscle activity are small during quiet breathing, having been estimated in terms of oxygen consumption to be about 0 5 ml. O_2/L of ventilation *Oxygen cost of breathing*[22-23] is estimated as the increase of total body oxygen consumption above the basal rate when the subject breathes

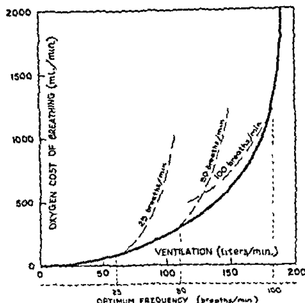


FIG. 8.—Normal oxygen cost of breathing related to ventilation and respiratory frequency There is an appropriate optimal respiratory frequency for each level of ventilation in the sense that oxygen cost is least at that frequency. The heavy line represents the variation of this minimal oxygen cost with increasing levels of ventilation (From the data of Bartlett and co-workers,[36] Liljestrand,[37] and McKerrow and co-workers [38])

at various increased levels of ventilation. Even though there are numerous ill-defined *factors* affecting the *oxygen cost of breathing*, the approximate relationships are essentially as shown in FIGURE 8. The sharp, nearly tenfold rise in oxygen consumption at maximal levels of ventilation reflects not only maximal respiratory muscle activity but also other nonrespiratory muscle activity. The curves of FIGURE 8 also show that with respect to the *oxygen cost of breathing* there is an apparent *optimal frequency* for any level of ventilation. Attempts also have been made to relate the energy expenditure of breathing to mechanical work, much as the engineer assesses the energy requirements of a machine. Although this approach is less applicable to muscles than it is to machines, it is nevertheless useful for reasons that will become apparent. The physicist and engineer have assigned a limited meaning to the term mechanical work, namely, force acting through distance. This is done so that work will be thermodynamically equivalent to other forms of energy. We know that muscle energy

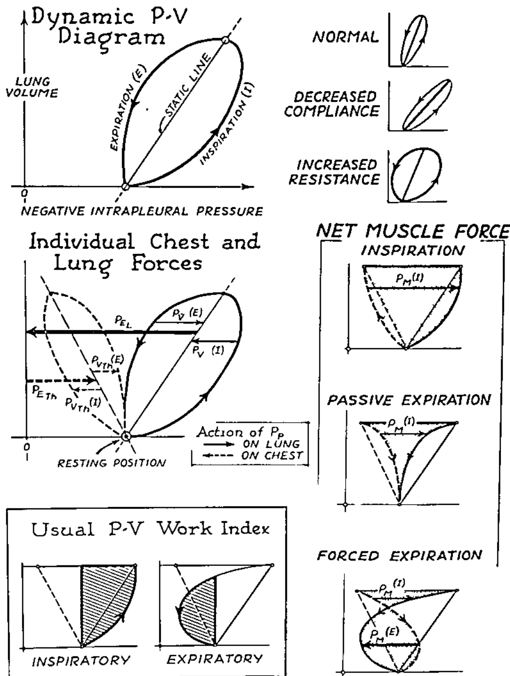


FIG 7 —*Dynamic pressure volume diagrams* Discussion of this figure is largely presented in the text In the center figure, for convenience, the symbol P_V is used to indicate the sum of $P_{V_{air}}$ [illegible] pressure during [illegible] To com- [illegible] ive chest recoil pressure corresponds to negative intrapleural pressure The P-V work index is shown as determined at the end-expiratory or relaxation volume (FRC) If the loops were actually recorded at different volumes above or below the relaxation volume, appropriate corrections would have to be made to account for the added work

lung and the chest at any instant. In the center and right hand portion of FIGURE 7, all of the integrated chest, lung and muscle forces have been shown. The individual forces active on the lungs, shown as solid lines, can be derived from intrapleural pressure-volume data but those individual forces active on the chest wall cannot be directly derived from the intrapleural

pressure-volume loop, having to be inferred from other data obtained on paralyzed or "completely relaxed" subjects; however, for completeness, a hypothetical P-V loop for the chest wall has been included as a dashed loop and the individual chest forces (not including muscle force) have been represented as dashed lines. The direction of the arrows indicates the direction of the forces. The net muscle force at any instant during respiration is that which opposes the algebraic sum of the individual chest and lung forces. The term net muscle force is used to indicate that both inspiratory and expiratory muscle forces may at times act simultaneously. During normal inspiration the net inspiratory muscle force as shown probably represents total force, since there is no evidence of significant restraining expiratory muscle effort. During passive expiration there exists a certain amount of residual inspiratory muscle force which must be overcome by forces of chest and lung recoil. This is indicated in FIGURE 7 by the fact that the algebraic sum of the individual chest and lung forces during a passive expiration is not zero. At least part of this muscle force appears to be an active restraining muscle effort,[6] but it is not clear how much represents some kind of inability of active muscles to relax instantaneously. During a forced expiration, active expiratory muscle effort, which increases expiratory flow, is reflected as a shift of the expiratory intrapleural pressure curve toward a more positive pressure. Additional shift may occur as a result of diminished restraining inspiratory force. Thus, total expiratory force is the net force shown in the diagram, plus any amount needed to overcome persisting inspiratory force.

The remainder of FIGURE 7 deals with the mechanical work and will be discussed in the next section.

Energy and Work of Breathing

The energy requirements of respiratory muscle activity are small during quiet breathing, having been estimated in terms of oxygen consumption to be about 0.5 ml. O_2/L. of ventilation. *Oxygen cost of breathing*[22-28] is estimated as the increase of total body oxygen consumption above the basal rate when the subject breathes

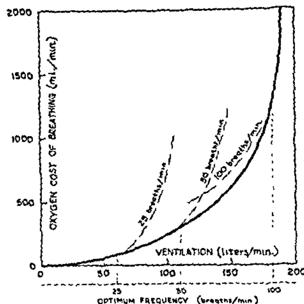


FIG. 8.—Normal oxygen cost of breathing related to ventilation and respiratory frequency. There is an appropriate optimal respiratory frequency for each level of ventilation in the sense that oxygen cost is least at that frequency. The heavy line represents the variation of this minimal oxygen cost with increasing levels of ventilation. (From the data of Bartlett and co-workers,[26] Liljestrand,[27] and McKerrow and co-workers.[28])

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is required to hold up a heavy object even though mechanical work in the sense of force times distance is not being performed. However, Fenn[29] has pointed out the general way in which muscle energy consumption is related to mechanical work and tension. During isometric contraction muscles require energy to exert tension but are not performing mechanical work on their surroundings. While shortening, muscles perform mechanical work and consume more energy than during isometric contraction at the same tension While lengthening, less energy is required to maintain a given tension as mechanical work is performed *on* the muscles. Hence, muscle energy requirements during breathing will be determined partly by average total tension exerted and partly by mechanical work done during motion

Mechanical work related to respiratory muscle activity is customarily expressed as volume change times pressure Thus, the stippled areas on the P-V diagrams (FIG 7, right) are graphic representations of respiratory P-V work corresponding to net muscle force It is not feasible to obtain such complete diagrams in actual practice, since there is no method of determining lung, chest and muscle forces simultaneously Otis[30] originally measured P-V work of breathing on "completely relaxed" subjects in a respirator so that respirator pressure was substituted for active muscle force Most subsequent investigators have measured intrapleural pressure, which gives no direct indication of individual chest and muscle forces but, rather, shows *net* action of muscles plus or minus chest forces on the lungs P-V work is determined in the manner illustrated in FIGURE 7, bottom left. This consists of calculating P-V work on the basis of variations in lung forces rather than muscle forces, so that the cross-hatched areas shown as indexes of P-V work correspond only to a portion of the area shown as net muscle force in the diagrams appearing on the right side of the same figure A total P-V work index is the sum of inspiratory and expiratory areas. Total nonelastic P-V work on the lung, not shown as such in the diagram, is represented by the total area within a complete P-V loop "Elastic P-V work," also not shown, is arbitrarily defined as the difference between the total P-V work index and measured nonelastic work

It must be emphasized that, just as the purely arbitrary method of using a P-V work index as an expression of energy expenditure of breathing is useful because it happens to correspond in a reasonably constant fashion to actual muscle work, the arbitrary use of components of the P-V work indexes in the manner just described has been found by some investigators to be useful to indicate certain empirical relationships between changes in compliance and resistance and changes in muscle work. The total nonelastic work does not make up more than 35 to 40 per cent of the total work index in normal subjects at ordinary tidal ventilation. At a given level of alveolar ventilation, the work corresponding to static recoil ("elastic work") is greater at low respiratory frequencies because of the greater static recoil at larger tidal inspirations The work corresponding to dynamic forces (nonelastic work) is greater at higher respiratory frequencies because frictional resistance is greater at the larger total ventilations necessary to maintain a specified alveolar ventilation The result, according to Otis and co-workers,[30] as well as McIlroy and co-workers,[31] is that the total P-V work index is minimal at a respiratory rate which often happens to correspond to the respiratory rate subjectively chosen by the subject Similar studies on the relation between FRC and work index[32] have shown that the total P-V work index is minimal at the resting mid-position during quiet breathing

The energy equivalent of one ml of oxygen utilization at a respiratory quotient of 0 85 is about 5 calories or 2 kilogram-meters of mechanical work [33] Available information on P-V work and the *oxygen cost of breathing*[34-39] would indicate a muscular efficiency for respiratory muscles in the order of 5 to 15 per cent One Kg.-M. of measured P-V work is equivalent to about 5 0 ml. of oxygen, at 10 per cent efficiency. A curve showing the relationship between ventilation and P-V work or the equivalent oxygen consumption at both 5 and 10 per cent muscle efficiency is shown in FIGURE 12.

In summary, the P-V work index is a means of relating respiratory muscle effort and energy

consumption to mechanical behavior of the breathing apparatus, but its usefulness is fundamentally limited because mechanical work does not account for the energy requirements of isometric contraction and because, at best, only net muscle force can be measured as pressure. Moreover, precise definition of the various areas of the P-V diagram representing work is not possible and, when attempted, is arbitrary. A clear understanding of our present-day knowledge of energy and work relationships is complicated by considerable confusion of definition in the literature. *Oxygen cost of breathing* is a direct measure of total energy requirements, but cannot be measured accurately enough to reflect small changes in respiratory work and is subject to variation from various metabolic determinants acting on the entire body.

Disturbances of Breathing Mechanics

A wide variety of diseases may alter the balance of forces concerned with ventilation. It is not our purpose to discuss each of these in detail but, rather, to show how general principles of pulmonary mechanics discussed in the preceding sections may be applied to the interpretation of disease states. The following functional classification of disorders has been made, with representative examples.

Weakness of Respiratory Muscles

Primary loss of muscle mass (*debility*, dermatomyositis)
Disorders of muscular *contractility* (*muscular* dystrophy, hypokalemia)
Disorders of myoneural transmission (myasthenia gravis)
Nervous disorders (Landry-Guillain Barré syndrome, poliomyelitis)

Disturbances of Thoracic Structure and Recoil

Reduced thoracic compliance and/or narrowed limits of distensibility
    Spinal and thoracic deformities (kyphoscoliosis, pectus [illegible]
    Crushing injuries of the chest
    Thoracoplasty
    Diaphragmatic herniation
External thoracic compression (obesity, ascites)

Disorders of the Pleural Space

Air or liquid in the pleural space (pneumothorax, hydrothorax, etc.)
Decreased pleural distensibility (pleural fibrosis)

Disorders of Mechanical Response Within the Lung

Functional loss of complete lung units
    Atelectasis or consolidation
    Small airway occlusion with distal air trapping (pulmonary edema, asthma)
    Parenchymal necrosis and fibrosis (pulmonary tuberculosis)
    Surgical resection
Increased airway or tissue frictional resistance
    1 Central airway obstructions (abductor paralysis of the vocal cords)
    2 Peripheral airway obstruction (bronchial asthma, emphysema)
Loss of elastic recoil (pulmonary emphysema)
Decreased distensibility of lung units
    Alveolar or interstitial fibrosis
    Pulmonary congestion and edema
Unequal distribution of ventilation

Weakness of Respiratory Muscles

Because of the functional overlap between the various groups of respiratory muscles and the large functional reserve provided by the accessory muscles of respiration, weakness or paralysis must be extensive before ventilatory failure ensues at rest. As an example of this, Hemingway et al [39] demonstrated that patients who have had cervical cord transections below the origin of the phrenic nerves can develop vital capacities and maximal breathing capacities between 50 and 70 per cent of normal. The principal muscle still functioning in these patients is the diaphragm, aided in varying degrees by accessory muscles of the neck and shoulder girdle. On the other hand, Lemon[40] has shown that exercise tolerance in dogs after total diaphragmatic paralysis remains apparently unimpaired, and Werner[41] showed that unilateral phrenicotomy in man may cause

negligible loss of ventilatory function after compensation has fully developed.

The existence of a weak, ineffective cough and a restricted tidal volume are important predisposing causes of secondary disturbances within the lungs of partially or totally paralyzed patients. Such patients are more susceptible to occlusion of airways, pulmonary atelectasis, and lung infections.

Disturbances of Thoracic Structure and Recoil

Thoracic compliance. Few direct measurements of static pressure-volume relationships for the thorax have been attempted in disease states because of technical difficulties, however, clinical observations and other pathophysiologic correlations allow us to make reasonable deductions. In kyphoscoliosis, for instance, severe spinal deformity markedly disturbs the positioning of the ribs and orientation of their axes of movement. Ribs are crowded together on the concave side of the spinal curvature and widely separated on the convex side. This must reduce the range of rib motion as well as unfavorably alter the mechanical advantage of intercostal muscles. It is likely that both the shape and volume limits of the static pressure-volume curve of the chest are altered by kyphoscoliosis. A practical appreciation of this may be obtained by attempting to perform a vital capacity while flexing the spine maximally to one side. Expansion of the thorax in these patients is not symmetrical and the resulting nonuniform distention of the underlying lung is apparent in pathologic specimens.[42] This probably causes unequal distribution of both alveolar ventilation and capillary perfusion. Secondary changes in mechanical properties of the lungs have been demonstrated[43] which are probably the result of distortion, narrowing and occlusion of airways, secondary atelectasis and pulmonary fibrosis.

In ankylosing spondylitis, the vital capacity and total lung capacity are reduced, apparently by restriction of the costovertebral joints. The lungs are apparently normal otherwise in this disease.[44]

The physiologic problems of kyphoscoliosis and ankylosing spondylitis are further discussed in chapter 43.

Thoracic supporting function. The thoracic walls serve as a semirigid supporting framework upon which respiratory muscles can exert an effective force and provide uniform lung expansion. When a part of this framework is lost by injury, congenital anomaly (absence of one leaf of the diaphragm), or surgical procedure (thoracoplasty), complete or partial collapse of the underlying lung will result and the unsupported lung is predisposed to paradoxical ventilation, i.e., it might expand while over-all lung deflation is occurring and vice versa. The latter paradox causes an ineffective pendular movement of air within the lungs and if the defect is large, serious ventilatory failure will occur.

External thoracic compression. Pathologic compression of the thorax occurs most commonly as a result of obesity and usually is most apparent in the supine position in which the diaphragm is exposed to the larger hydrostatic pressure of the abdominal contents. Referring to FIGURE 3, a constantly increased weight or hydrostatic pressure acting on the thoracic walls theoretically would shift the static chest and total recoil curves to the right, along the pressure axis, without changing the curve shapes. The most important consequence of this is a shift of the resting lung mid-position (zero pressure intercept in the figure) to a lower lung volume, this is really an exaggeration of what occurs when a normal person changes from the upright to a supine position. At the smaller resting lung volume, intrapleural pressure is more positive and lung airways are narrower and more susceptible to surface tension effects and sudden occlusion. Therefore, secondary changes in the shape of the lung recoil curve, as well as increases of airway frictional resistance, may occur.

Disorders of the Pleural Space

Introduction of air or fluid into the potential pleural space causes the chest to expand and the lung to deflate until a new position of static equilibrium is achieved. Referring again to FIGURE 3, this has the effect of shifting the static chest P-V curve downward along the lung volume axis which is in contrast to the shift along the pressure axis produced by obesity or ascites. Theoretically the slope of

the chest and lung recoil curves should not be altered, but their limits of volume change (dotted extrapolations in Fig. 3) are brought *closer* together so that the thorax becomes more important in limiting inspiration while air trapping in the lung may limit expiration.[45] The *resting mid-position* of the lung will be at a smaller volume, therefore, secondary changes in airway resistance and lung compliance are a probable consequence, just as in obesity

If pleural fluid becomes organized, it is obvious that both the slope and volume limits of the static P-V curve will be changed in such a way that combined chest and lung compliance may be greatly reduced

Disorders of Mechanical Response Within the Lung

These are summarized graphically in Figures 9, 10 and 11.

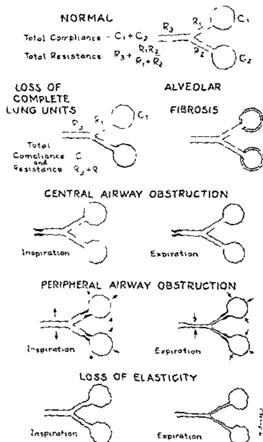


Fig 9.—Schematic summary of mechanical disturbances *within the lung*.

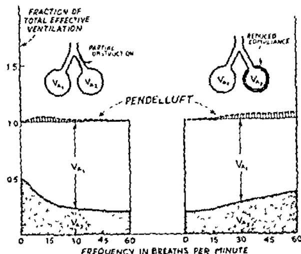


Fig 10.—Unequal distribution of mechanical disturbances, breathing frequency, and the distribution of ventilation. Arbitrary numbers were assigned for compliance and resistance of the schematic lung units

	Compliance	*Resistance*
$\dot{V}_{A_1}$	0 1	4
$\dot{V}_{A_2}$	0 1	16
$\dot{V}_{A_3}$	0 025	4

Distribution of ventilation within each portion of the paired units was estimated by the electrical analogy proposed by Otis et al [48], assuming that the driving pressure for ventilation is *applied* as a sine wave function of time The pendelluft is the ineffective exchange of air back and forth between the paired components In essence, when unequal distribution of airway resistance exists in the presence of uniform distribution of compliance, ventilation becomes more uniform as the breathing frequency is slowed When *unequal distribution of compliance exists in the presence of uniform airway resistance*, ventilation becomes more uniform as the breathing frequency becomes greater If there is a uniform distribution of the products of resistance and compliance for individual lung units, ventilation may still be unequal but its distribution will be independent of breathing frequency.

Occlusion or loss of lung units It has been mentioned in a previous section that airway resistance and lung compliance are dependent upon the total number as well as the dimensions of functioning airway-volume units. Thus, if complete units (alveoli and supplying airways) are functionally lost, airway resistance will increase as lung compliance decreases even though the dimensions and mechanical properties of the remaining units may be unchanged. The effect of functional loss of respiratory units on airway resistance depends in part upon the

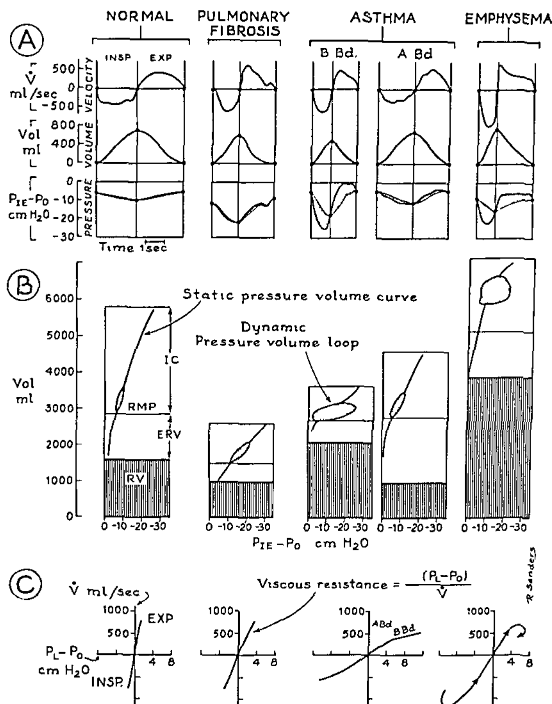


Fig 11.—*Static and dynamic pressure-volume relationships in patients with representative lung disorders* Row (A) shows simultaneous recordings of air flow velocity at the mouth, tidal volume, and esophageal minus mouth pressure ($P_{ie} - P_o$) during a single breath Esophageal pressure has been utilized as an estimate of pleural pressure The heaviest line in the pressure tracing represents the recorded value of ($P_{ie} - P_o$), whereas the thin line has been added to indicate the elastic pressure of the lung (P_{EL}) estimated from the instantaneous level of lung distention The width of the stippled areas between these lines at any instant represents the pressure difference required to overcome viscous (nonelastic) resistance ($P_L - P_o$) When ($P_L - P_o$) is plotted against corresponding air flow, the resistance lines in (C) result The [illegible] enclosed within the dynamic pressure-volume loops in (B) represent the P-V

work is increased.

airway level at which the occluded units arise. Thus, TABLE 3 indicates that less increase of resistance can be expected from occluding 50 per cent of the small peripheral airways and their distal alveoli scattered throughout the lung than from occluding the major bronchus to one lung, whereas loss of compliance is more closely related to the alveolar volume lost than to the level of occlusion.

Lung units are functionally lost as a result of consolidative processes, parenchymal necrosis and fibrosis, surgical resection, or as a result of primary occlusion of airways. Lobar and confluent bronchopneumonia provide common examples of the consolidative process, and pulmonary tuberculosis is a common example of parenchymal necrosis and fibrosis. Occlusion of segmental or more central bronchi with well-defined atelectasis distal to the occlusion is the most commonly recognized form of airway occlusion, but occlusion of smaller, more peripheral airways is probably more frequent and possibly the most frequent cause of lung unit occlusion. Because it is less frequently recognized, the latter mechanism will be considered in greater detail.

Small airways may be predisposed to occlusion by forces of compression from outside the airway, by excessive smooth muscle tension in the airway wall, and in very small airways by the effects of surface tension at the air liquid interface of the airway wall. Airways are also frequently occluded by foreign material such as pus in the lumen, in very small airways, however, surface forces are important in maintaining occlusion[15] once present, no matter what the cause, unless fibrous organization has occurred (bronchiolitis obliterans). Occlusion may be permanent or temporary and air may be excluded or trapped distally. Trapped air always will be absorbed slowly by venous blood entering the surrounding tissue, and, in time, collapse of the entire volume unit will occur unless collateral ventilation is sufficient to sustain expansion or unless occlusion is intermittent. This is important because once distal air absorption has occurred, greater energy then will be required to re-expand the unit. Temporary or intermittent occlusion of small, unsupported airways probably occurs to some extent during normal ventilation and accounts for much of the static hysteresis of the lung recoil curve, as previously discussed under static forces (surface tension). It is more likely to occur whenever the diameters of airways are narrowed by bronchospasm, by structural changes in the airway wall, or by increased quantities of liquid in the airway lumen, and consequently it is probably a common occurrence in severe bronchial asthma,[46-48] bronchopneumonia and pulmonary edema.[49] It probably occurs in lungs compressed by obesity, pneumothorax and hydrothorax.[50] Recently, it has also been suggested that the primary lesion in pulmonary emphysema is obliteration of small respiratory bronchioles but that alveoli distal to the occlusion continue to be ventilated poorly through collateral channels.[51] With this concept of the pathogenesis of emphysema, disruption of alveolar septa and loss of elastic recoil are important secondary phenomena.

Mechanisms essential for maintaining patent airways concern the ability to take a deep breath or at least to distend airways with high negative intrapleural pressures, and the ability

TABLE 3.—*Estimated Effect of Occluding 50 Per Cent of the Airways at Different Levels on Lung Compliance and Resistance to Laminar Air Flow**

Level of Occlusion	Resistance to Laminar Flow (cm H_2O/L./Sec.)	Compliance (L./cm H_2O)
Unoccluded	2.00	0.2
Major bronchus	3.75	0.1
Bronchus to secondary lobule†	3.24	0.1
Respiratory bronchioles of third order†	2.66	0.1

* Estimated with Rohrer's calculated data on the fraction of total resistance offered by the different airway components between the alveoli and the pharynx.[18]

† Over-all resistance and compliance would be higher than quoted if units distal to occluded airways were collaterally ventilated through adjacent units having patent airways. On the other hand, loss of volume in completely occluded units would result in compensatory overdistention of the remaining airways and alveoli until a new point of balance between lung recoil and thoracic recoil was achieved and tend to minimize the over-all increase in airway resistance and to aggravate the decrease of lung compliance.

to achieve high linear air velocities during a cough[52-54] Both mechanisms are deficient in patients with muscular weakness or paralysis, and multiple airway occlusion may account in part for the loss of lung compliance which occurs rapidly following respiratory paralysis in the acute stages of poliomyelitis[55] The probable importance of being able to take an occasional deep breath is illustrated most convincingly by the prominent (hysteresis) loops in the pressure-volume diagrams of the lungs as shown in FIGURE 4 Integrated ciliary action in the bronchial mucosa and an effective cough are necessary for raising excessive secretions from peripheral airways For a cough to be satisfactory, it is necessary that elastic units peripheral to the obstruction be distended with air so that an adequate expulsive pressure gradient will occur, and a high velocity of airflow is required in those airways convergent with the obstructed airway so that material expelled will be forcefully moved into more central channels Patients who, for any reason, cannot produce rapid expiratory velocities have ineffectual coughs These are noted in patients with pulmonary emphysema and bronchial asthma as well as patients with muscular weakness of the abdomen and thorax

Increased frictional resistance and loss of lung elastic recoil Increased frictional resistance to breathing is most often caused by narrowing or occlusion of airways Narrowing may be a primary anatomic change or a secondary one caused by alterations in pressure fluctuations acting upon or within the bronchial walls during a breath, thus predisposing to greater than normal fluctuations in lumen diameter Primary narrowing of airways which is localized at a given level may redistribute the pressures applied to otherwise unaffected airways at other levels and alter the normal fluctuations of airway resistance which occur during a breath. These altered patterns of fluctuation in airway resistance are critically dependent upon location and character of the primary disturbance. Thus, it is generally recognized that narrowing of peripheral airways causes an exaggerated increase of resistance during exhalation but that narrowing of more central air passages, such as the trachea or larynx, causes nearly equal increments of resistances during both phases of a breath. Loss of lung elastic recoil results in poor elastic support of airways and consequently also predisposes to exaggerated expiratory airway narrowing and increased expiratory resistance

A better understanding of the causes and secondary effects of airway narrowing may be gained by considering the pressures to which airways are subjected and how these pressures may be altered by disease. The air passages are immediately surrounded by alveolar pressure which may act to narrow or distend airways depending on the phase of respiration Elastic tension within the fine septal tissues of the lung continuously maintains a distending pressure on the airways Pressure in the airway lumen resists collapse during expiration and resists distention during inspiration The sum of pressures acting on a small segment of airway wall can be analyzed in an algebraic manner as follows

$$\text{wall stress} = P_A - P_{lumen} - P_{EL} \qquad (1)$$

P_A and P_{EL} = alveolar pressure and elastic recoil pressure of the lung, respectively

P_{lumen} = airway lumen pressure

The algebraic signs have been chosen arbitrarily, pressure gradients acting to expel air from the lungs are considered positive and those acting in the opposite direction are considered negative. Then, if we represent pressure exerted by active or passive tension in the airway wall by P_w, the effective pressure tending to distend or collapse an airway at any instant may be written as follows

Effective transmural pressure

$$= P_A - P_{lumen} - P_{EL} + P_w \qquad (2)$$

P_w may be either positive or negative, depending on the state of stretch in the wall; when the wall is under stretch, P_w is positive, but some point of narrowing must exist where elastic structures in the wall become relaxed and beyond which further narrowing results in elastic tension resisting collapse[56]; when the latter occurs, P_w in our scheme becomes negative Smooth muscle tone and surface tension may also contribute significantly to P_w. The term

$(P_A - P_{lumen})$ represents the pressure drop from the alveoli to the airway segment being considered, therefore, Equation 2 also may be written as follows:

$$\textit{Effective transmural pressure} = R_p\dot{V} - P_{EL} + P_w \quad (3)$$

R_p represents the frictional resistance *peripheral* to the airway segment being considered

$\dot{V}$ represents the rate of air flow to the segment It becomes apparent, then, that an airway is more susceptible to narrowing during expiration if either the peripheral resistance (R_p) or the rate of air flow ($\dot{V}$) is high, if the elastic recoil of the surrounding lung (P_{EL}) is low or if the negative recoil pressure exerted by the airway wall (P_w) to resist collapse is small In bronchial asthma, a primary increase of frictional resistance in peripheral airways occurs as a consequence of narrowing by bronchospasm or occlusion by thick mucus In pulmonary emphysema, loss of lung elastic recoil and/or structural changes in bronchiolar walls which lower their elastic resistance to collapse may be important changes,[57, 58] which are superimposed upon narrowed or occluded peripheral airways Exaggeration of the increased nonelastic resistance during expiration is a more prominent and consistent finding in pulmonary emphysema than in bronchial asthma [59] The work of Campbell, Martin and Riley[21] suggests that either the primary narrowing or occlusion of airways in pulmonary emphysema is more peripherally located than in bronchial asthma or the airways of asthmatics have more rigid walls which are more resistant to narrowing and collapse Pathologic evidence might be cited for both of these suggestions [45, 51, 60]

More centrally located airways have thicker walls and cartilaginous support which makes them less susceptible to collapse[56], therefore, when partial airway obstruction is located in the more central airways, fluctuations in airway resistance due to expiratory airway narrowing are less marked.

A pressure gradient larger than $(P_{EL} - P_w)$ to a given small airway segment cannot be sustained without causing complete collapse of the segment. This means that an effective upper limit of air flow is imposed which cannot be exceeded even though greater expiratory pressures are applied [21, 54] If $P_{w_{max}}$ is assumed to represent the maximal negative pressure with which the wall of the airway segment can resist collapse, the maximal pressure gradient to the airway segment from the alveoli would be as follows:

$$(P_A - P_{lumen})\ max = P_{EL} - P_{w_{max}} \quad (4)$$

Further increases of intrapleural pressure after this gradient has been reached would increase P_A and P_{lumen} to the same extent without changing the pressure difference. This can be restated in terms of flow by rearranging equation 3 for a state of equilibrium as follows.

$$\dot{V}_{max} = \frac{P_{EL} - P_{w_{max}}}{R_p} \quad (5)$$

Those small airway segments in which $\dot{V}_{max}$ is reached earliest at a given lung volume during a forced exhalation collectively will determine $\dot{V}_{max}$ for the entire lung As lung deflation proceeds, $\dot{V}_{max}$ falls since lung elastic recoil (P_{EL}) becomes less and peripheral airway resistance (R_p) increases As airways shorten during exhalation, elastic resistance of the airway walls to collapse ($P_{w_{max}}$) may also decrease. Attempts by the subject to increase expiratory flow beyond this maximal level at any given lung volume by increasing expiratory effort may actually reduce the rate of air flow achieved[55]; therefore, a point of diminishing returns is reached as expiratory force is increased (Fig 16) In patients with asthma and emphysema, $\dot{V}_{max}$ may be reduced to levels of air flow which are frequently achieved during normal quiet breathing.[54]

Reduced distensibility of lung units In alveolar or interstitial fibrosis, lung units become encased in a thick, collagenous net which reduces compliance and limits distensibility In pulmonary congestion, the pulmonary vascular net becomes distended with increased amounts of blood, and it is conceivable that the increased static tension within the vessel wall offers greater than normal elastic resistance to deformation, as a consequence, the compliance of lung units may be reduced. However, acute pulmonary congestion, whether it involves pulmonary arterial hypertension or primarily

capillary-venous hypertension, has been shown to cause only a slight decrease in lung compliance unless pulmonary edema has supervened [60, 61] Congestion will replace an equivalent amount of air from the lungs and thereby may reduce the volume of air which can be contained at maximal inspiration, but this effect does not imply necessarily a change of compliance in the normal breathing range of lung volume. *Pulmonary edema reduces compliance* by occluding peripheral units from effective ventilation[49], it probably does not alter distensibility of units which do not contain intralumenal edema fluid and which have patent airways supplying them The low lung compliance noted in patients with chronic pulmonary congestion without apparent pulmonary edema probably is caused by secondary vascular and other parenchymal changes in the lung[63, 64] or by subclinical amounts of edema fluid

Unequal distribution of ventilation When altered mechanical properties in the lung or thorax are not uniformly distributed, inequalities of ventilation occur (Fig 10) If the ratio of ventilation to perfusion remains uniform, unequal distribution of a mechanical derangement has no more effect upon pulmonary function than would be expected from a uniform mechanical disturbance producing the same over-all change in lung frictional resistance and compliance. If the ratio of ventilation to perfusion is nonuniform, the efficiency of ventilation in terms of gas exchange is impaired Thus, to achieve the same effective alveolar ventilation, a greater total ventilation and consequently more ventilatory work must be performed than would be expected for a similar disturbance of mechanical function which is uniformly distributed. Also, arterial oxygen desaturation, which cannot be compensated even by increasing total alveolar ventilation may occur.

Nonuniformity of ventilation is a frequent occurrence, as would be expected, since pulmonary disease is seldom distributed uniformly. It is probably most abnormal in patients with pulmonary emphysema and chronic bronchial asthma in whom the primary disturbance is an unequal distribution of airway resistances. In such conditions, knowledge concerning the relationship between breathing frequency and distribution (Fig 10) may have practical therapeutic importance. When therapeutic aerosols are being administered, patients should be instructed to breathe slowly and, if possible, pause at the end of inspiration[65] to improve the distribution of medication. Also, one benefit of proper breathing exercises in patients with *pulmonary emphysema may be to slow the rate* of breathing and in this way to improve the distribution of respired air Whether or not more uniform distribution of ventilation is beneficial in terms of gas exchange, however, depends upon the associated distribution of alveolar capillary blood flow, as mentioned above Thus, an increased frequency of breathing might improve the distribution of ventilation to areas of reduced unit distensibility, as shown in Figure 10, but the pathologic process which has altered distensibility may have simultaneously restricted the local vascular bed and, *in such an instance, improved distribution* of ventilation may only serve to increase physiologic dead space and impair ventilatory efficiency

Dyspnea and Pulmonary Mechanics

Dyspnea is a complex subjective sensation most often described by patients in terms of increased awareness of added respiratory effort It may exist in the presence of either increased or decreased ventilation Many physiologists and clinicians feel that the work of breathing must play a significant role in causing dyspnea [66] Marshall, Stone and Christie[1] have indicated, as mentioned previously in this Chapter, that mechanical work, as understood by the physicist, is an incomplete index of total respiratory effort. They found that a patient with mitral stenosis, a patient with pulmonary emphysema, and a normal subject whose airway was severely obstructed, exhibited less P-V work, and total oxygen consumption at levels of maximal tolerated exercise than did a normal (unobstructed) subject. Thus, the effort of breathing expressed by these parameters could not be considered the limiting factor for exercise. On the other hand, the mean *inspiratory pressure* was essentially the same

both in the patients and normal subjects under the same circumstances. Whether mean pressure is a better index of muscle effort remains to be determined. In several instances, such as patients with severe muscular paresis, curarization, or intercostal neuritis, severe dyspnea may be experienced when there is little or no respiratory muscle effort involved in breathing.[67] McIlroy[68] has made a reasonable hypothesis that the sensation of dyspnea is most nearly related to respiratory muscle oxygen debt. It seems likely that, under certain circumstances, direct chemical stimuli and chemoreflexes, as well as other mechanical reflex stimuli from the respiratory apparatus and other parts of the body must play either a major role in causing the sensation of dyspnea or in conditioning the patient so that respiratory muscular effort alone or in relation to oxygen supply becomes the immediate causative factor. The subjective aspect of dyspnea introduces an inestimatable variability into any evaluation of its mechanisms.

The Work of Breathing and Chronic Obstructive Disease

In patients with severe obstructive disease, such as pulmonary emphysema, in whom alveolar ventilation is no longer adequate to maintain normal arterial CO_2 tension, the greatly increased work of breathing with respect to any level of ventilation places a major limitation on activity tolerance and ventilatory capacity. Under these circumstances, the optimal level of ventilation for CO_2 excretion may be quite low, and any increase in ventilation above the optimum causes CO_2 production in excess of the excretion rate, the net effect being exaggeration of the respiratory acidosis.[69-70]

The relationship of the work of breathing to the "hypoventilatory" response associated with oxygen breathing under circumstances of severe ventilatory insufficiency (emphysema, kyphoscoliosis, obesity, etc.) requires further clarification. Cherniak[70] demonstrated that normal subjects also retain carbon dioxide when they breathe against an external resistance of the same magnitude as the intrinsic resistance observed in asthma or emphysema patients who have CO_2 retention, this emphasizes the important role of respiratory mechanical factors in the control of arterial CO_2 tension. Thus, under certain circumstances, respiratory stimulation as a therapeutic measure may be not only ineffective but also detrimental if the increased ventilation results in more CO_2 production from the work of breathing than can be effectively eliminated. The more direct, primary approach to the problem of respiratory acidosis is to decrease airway resistance,[70] decrease the work of breathing, and improve effective alveolar ventilation by the use of bronchial dilator drugs, detergents, surface active compounds, and antibiotic agents in conjunction with respiratory mechanical assistance. The effect of these measures on the P-V work, as well as the oxygen cost of breathing, is graphically illustrated in Figure 12, where the work with respect to any level of ventilation is shown to be very high in a patient with obstructive pulmonary disease. After a single treatment with an aerosol bronchodilator agent, the level of work at any given level of ventilation is greatly reduced. This was also demonstrated in another way in Figure 11B, where the area within the dynamic P-V loop, indicative of respiratory work, is seen to decrease dramatically after an aerosol bronchodilator drug.

In some instances, obstruction is not reversible and is dependent largely on the interrela-

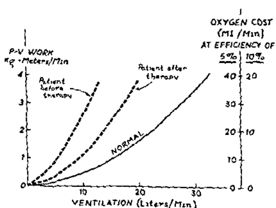


Fig 12.—Relationship of P-V work and oxygen cost of breathing to ventilation. Measured P-V work index in a patient with severe obstructive disease before and after therapy is compared to average data from normal subjects. The equivalent oxygen cost at two assumed efficiencies is indicated at the right.

tionships of airway resistance and lung recoil, as discussed in a foregoing section If the $\dot{V}_{max}$ is so low that it is just possible for the patient to maintain sufficient ventilation for a resting metabolic level, then CO_2 retention will occur if any attempt is made to increase airflow by greater respiratory effort. When such patients become dyspneic or excited, they often perform expiratory efforts which exceed those necessary to achieve maximal rates of flow, as a consequence, they may exert large amounts of effort to achieve less than maximal ventilation Such patients may be helped by being taught to moderate their expiratory efforts, and some probably achieve similar results spontaneously by pursing their lips during expiration and counterbalancing excessive expiratory effort which would otherwise reduce, rather than increase, the velocity of exhalation Howard Dayman[71] very concisely stated the dilemma that confronts the patient with severe pulmonary emphysema when he indicated " in this disease expiration is fixed by the check valve mechanism[57] and inspiration by the hyperinflated condition of the thorax The purpose of therapy is to enhance the efficiency of breathing within these fixed limits " Thus, the most important aspect of breathing training is the maintenance of a slow breathing rate[71, 72] designed to minimize what, in patients with obstructive emphysema, is the largest component of the increased work of breathing, that is, the dynamic, nonelastic work[58, 73-77] In some cases, it may be necessary to supply oxygen to make it possible for these patients to be active without resorting to inefficient increased respiratory effort[78] These therapeutic considerations are discussed in more detail elsewhere in this book

Relationship of Pulmonary Mechanics to Assisted or Controlled Ventilation

A problem of increasing current interest pertains to the significance of flow rate control in the use of pressure-limited, assisted or controlled respiration Just as rapid breathing rates will tend to result in uneven ventilation in patients who have nonuniform distribution of airway resistance, so will pressure-limiting assistors operating at high flow rates have essentially the same effect in such patients. High inspiratory flow rates cause the cut-off pressure of the breathing unit to be reached rapidly and inspiratory time to be correspondingly short, and the tidal ventilation correspondingly small[79, 80] Thus, proportionately less ventilation will gain access to the partially obstructed areas, while areas with low resistance will tend to be overinflated Apparatuses with adjusted slower flow rates or devices which function at variable flow rates (so called "flow sensitive" devices) are capable of prolonging inspiration and providing larger tidal volumes and more uniform distribution of inspired air.

There is little common understanding among physicians as to the meaning of the terms "flow sensitive" versus "pressure sensitive," used descriptively in regard to pressure breathing devices In the strict sense these units are all pressure sensitive in that a pressure gradient is required to establish and maintain flow. However, "pressure sensitive" devices generally operate at relatively high minimum flow rates so that the valve is either wide open or closed The so-called "flow sensitive" units operate at variable and low minimum flow rates so that the valves will stay partially open even though the flow into poorly ventilated units of lung is slow

Much information available tends to leave the impression that the physiologic effects of breathing assistors or respirators is a function of their physical characteristics alone The behavior of these instruments varies greatly in individual patients depending on the pattern of breathing and the type of mechanical disturbance characterizing their lungs[80] Moreover, since the mechanical properties of the lungs of seriously ill patients are apt to change even from moment to moment, the function of breathing aids is likely to change Thus, a constant re-evaluation of the pressure volume relationships of the patient's pulmonary apparatus is necessary to maintenance of proper respiratory exchange.

Although a thorough understanding of these considerations is of utmost importance, a detailed discussion of the clinical application of

these principles is not within the scope of this chapter.

Indirect Methods of Assessing Mechanical Function

Since direct measurements of pulmonary compliance and resistance do not lend themselves well to convenient clinical evaluation of ventilatory mechanics, it becomes a matter of more than casual interest that certain simple ventilatory function tests may be utilized.

The vital capacity is a measure of the maximal displaceable lung volume which, by and large, will reflect the balance of forces between muscular strength and elastic recoil. The maximal displaceable volume may be reduced not only as a result of reduction in pulmonary or extrapulmonary compliance but also as a result of extremely severe increases in airway resistance, so that lung units are effectively removed from the dynamic lung volume This change is conveniently reflected by a reduced functional* compliance Thus, a good correlation can be demonstrated between the vital capacity and compliance for normal individuals and for subjects with a variety of pulmonary ventilatory disturbances, (Fig. 13) The greatest discrepancy in this relationship occurs in patients with pulmonary emphysema in whom measured compliance tends to be high in relation to the vital capacity, particularly if the compliance is measured under static or near-static conditions

The data of Marshall et al,[82] Attinger et al,[83] and Cook et al,[19] obtained from a wide age range of normal subjects, all reveal an identical relationship for the functional compliance/vital capacity ratio, 0 035 ± 0 01 Frank et al[84] found the ratio static compliance/vital capacity to be essentially the same Attinger et al[81] found this relationship to hold also for patients exhibiting many types of ventilatory disturbances, again with the singular exception of patients with severe pulmonary emphysema. Because of large standard deviations, these relationships must be considered only gross estimates of the elastic properties of the lung in different individuals. However, when a patient is used as his own control, changes in vital capacity can be held as very acceptable evidence of comparable changes in pulmonary compliance Marshall et al[82] found an even better correlation (+0 904) of compliance to the functional residual capacity (FRC) The compliance/FRC ratio was 0 050 with a range of 0 038 to 0.070 This result has been confirmed by Cook et al[19] in children and young adults Moreover, they suggest the use of this ratio to ascertain whether changes in compliance can be attributed to reduction in lung volume alone or to a structural change in lung tissue. The compliance/vital capacity ratio could probably

* The term functional is used to indicate compliance measured during ordinary quiet breathing, as contrasted with static compliance measured by techniques involving intermittent interruption of respiration at different volumes in an attempt to insure a more nearly static, pressure-volume state

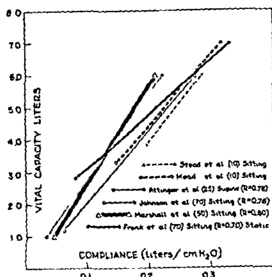


Fig 13 —Vital capacity—compliance The relationships of vital capacity, a measure of displaceable lung volume, to measured pulmonary compliance, as found by a number of investigators In each case the number of patients studied is indicated by the number in parenthesis after the author's name This figure illustrates the fact that there is an excellent linear relationship between functional compliance and vital capacity The same holds true for static compliance measurements in normal subjects The method of determining functional compliance appears to underestimate true compliance at larger lung volumes All the data shown are from normal subjects except for that of Johnson et al which includes in addition patients with a variety of ventilatory disorders This figure was taken from data published elsewhere[81]

also be used somewhat less satisfactorily for this purpose where functional residual capacity is not known.

Although patients with cor pulmonale[53] and right heart failure often show a decreased compliance and vital capacity, the compliance may be normal in contrast to the striking decrease in compliance noted in left heart failure with pulmonary congestion.[61] These findings tend to emphasize the fact that cor pulmonale does not affect vital capacity or compliance per se but that pulmonary changes which alter the vital capacity or compliance may also cause cor pulmonale.

There is insufficient data from the older age groups to draw any definite conclusions, but compliance may or may not decline with age. If aging were accompanied by decreasing elastance of the lung, the measured compliance would not be expected to decline with the vital capacity, but perhaps even increase.

The vital capacity is an estimate only of the static, elastic factors of mechanical function and thus yields no useful information concerning the more dynamic aspects of function affecting the velocity of volume displacement. Measures of air flow would be expected to bear an inverse relationship to pulmonary airway resistance or a direct relation to airway conductance. Very few studies of these relationships have been made. Perhaps this is in part a result of the lack of uniform agreement concerning the relative value of the various methods of estimating the velocity of volume displacement.

TABLE 4.—*Formulae for the Prediction of the Maximal Breathing Capacity*

Author	Sex	Prediction Formulae
Baldwin et al.[85]	males	[86.5 − (0.522 × age)] M² BSA
	females	[71.3 − (0.474 × age)] M² BSA
Motley[86]	males	(97 − (age/2)) M² BSA
	females	(83 − (age/2)) M² BSA
Needham et al.[87]	males	(−1.1 × age) + (40 × M² BSA) + 94
	females	(−0.7 × age) + 113
Miller et al.[88]	males	(109 − (age/2)) M² BSA
	females	(92 − (age/2)) M² BSA

The maximal breathing capacity (MBC) is the maximal volume of air that can be voluntarily displaced in a period of 12, 15, or 20 seconds while the subject breathes as deeply and as rapidly as he can. This test has been the most widely used method of estimating the velocity of ventilation. The predicted normal maximal breathing capacity can be derived from any one of a number of formulae from different laboratories (TABLE 4). The variability in these prediction formulae suggests that each examiner must compare his own results on normal subjects with those listed before any particular method is adopted.

Bartlett and co-workers[89,90] have studied the relationships between the maximal breathing capacity and added external resistances in normal subjects and found essentially an inverse sigmoidal relationship. However, the relationship of the MBC to changes in airway resistance is best illustrated by a large group of data from Attinger et al.,[53] including both normal subjects and patients with a variety of cardiopulmonary disorders. The data were treated so as to express the relationship between the MBC and conductance (FIG. 14). A fair positive correlation is apparent in spite of a great deal of scatter and some striking exceptions among patients with cardiopulmonary diseases. The inconsistency between the measured MBC and measures of airway resistance in patients is largely the result of the numerous variables determining the measured maximal breathing capacity. These factors, which have been elucidated by Bernstein,[91] Bartlett,[89] Miller[88] and their co-workers are: Neuromuscular training and coordination, breathing rate in relation to the level of airway resistance, the respiratory level at which breathing is performed, the relative time spent in reversing the direction of air flow, as well as nonpulmonary factors affecting patient willingness and ability to perform. Nevertheless, impaired airway conductance is a major limiting factor in the performance of the MBC.

More recently, measurement of specific timed segments of the forced vital capacities (FVC), identified as timed forced expiratory

capacities (FEC_t), have been utilized as indirect estimates of airway resistance.[31] A study in our laboratory[64] of the relationships of the FEC_t for 0.5 second, $FEC_{0.5}$, 0.75 second, $FEC_{0.75}$, and 1.0 second, $FEC_{1.0}$, to the MBC revealed excellent correlations for all the FEC_t determinations (+0.90 to 0.92) in normal subjects and patients with various disorders of pulmonary ventilation. The nonpulmonary variables previously mentioned probably account for the discrepancies that are occasionally observed in certain patients with pulmonary ventilatory disturbances. Reasonable estimates of the MBC can be obtained from the FEC_t determinations by multiplying the measured expiratory capacities by the appropriate factor derived statistically from the above data. These are:

$$FEC_{0.5} \times 53 = MBC_{est}\ L/min$$
$$FEC_{0.75} \times 46 = MBC_{est}\ L/min$$
$$FEC_{1.0} \times 41 = MBC_{est}\ L/min$$

An analysis of the relationship of the FEC_t to mean expiratory airway conductance indicates a very good positive correlation for the $FEC_{0.5}$ (FIG. 14). Again, because of fairly large standard deviations, these functions will find their greatest value in predicting changes in conductance when a patient is used as his own control, such as is illustrated in FIGURE 15. Thus, properly performed* FEC_t tests are probably more reliable estimates of air flow characteristics and thus airway resistance per se than is the MBC.

Various other methods of evaluating the dynamic functions of the lung have been suggested. Comroe[92] has proposed the measurement of "maximal" inspiratory and expiratory flow rates derived from the 200 to 1200 cc. volume segments of rapidly recorded vital capacity curves. Leuallen and Fowler[93] have suggested a comparable measurement of the flow rate over the mid-half of the forced expiratory vital capacity curve (maximal mid expiratory flow rate, MMF). These authors emphasize the importance of sustained high flow rates to ventilatory function. Patients

* Reproducibility is generally acceptable as the best criterion of reliability and thus maximal values for the FEC_t should be repeatable within 50 cc.

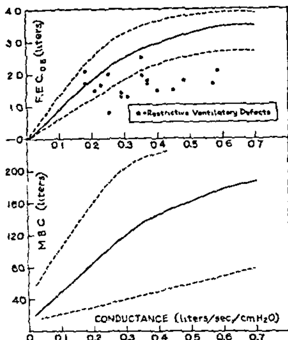


FIG. 14.—Relationship of the forced expiratory capacity (0.5 second) and maximal breathing capacity to conductance. (*Above*) The relationship of the 0.5 second forced expiratory capacity ($FEC_{0.5}$) to the mean resting pulmonary expiratory conductance. The solid line represents the visual line of best fit for the data from 70 determinations, while the dashed lines describe the limits of the scatter about the line. Also shown as solid circles is a group of patients with restrictive type ventilatory defects whose data are plotted against this graph to demonstrate that restrictive defects may result in a decrease of volume without a decrease in the number or area of the airways. Thus, cases with reduced $FEC_{0.5}$ values but high conductances in relation to this volume are the patients described as examples of pure restrictive ventilatory defects by the quadrant plot, FIGURE 18. (*Below*) The relationship of the maximal breathing capacity (MBC) to mean expiratory conductance. The solid line represents the visual line of best fit for the data from 100 determinations by Attinger,[83] while the dashed lines represent the limits of scatter about the line. It is apparent that there is greater scatter or variability for this relationship compared to that shown above for the $FEC_{0.5}$. This figure was taken from data published elsewhere.[61]

with pulmonary emphysema who show sudden sharp decreases in air flow shortly after initiation of forced expiration are the type of patient who reveals a marked reduction of the MMF. Shepard[94] has proposed a pneumotachographic measurement of maximal breathing capacity or peak flow rate as an effective

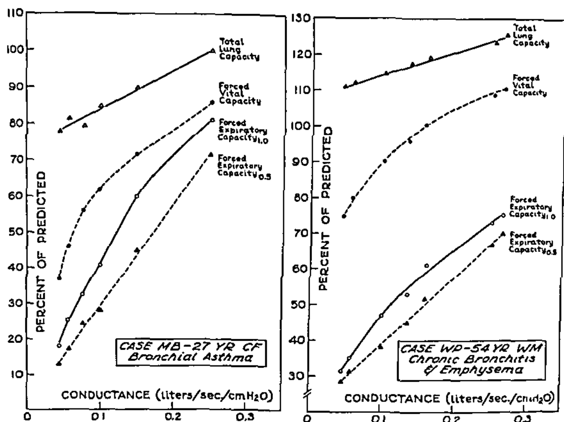


FIG 15 —*Lung volumes—conductance* The relationships between lung volume and mean expiratory pulmonary conductance in two patients followed over a period of two years during the course of treatment of their respiratory disorders are illustrated so as to demonstrate the strikingly linear behavior of the $FEC_{0.5}$ in relation to changes in conductance, as well as the more or less predictable behavior of other lung volumes In case M B (*left*) characteristic of uncomplicated asthma, there has been a fairly uniform change in the number of available lung spaces and airways, in striking contrast to case W P (*right*) who shows the typical changes of emphysema where a striking disparity exists between the available lung space and the capacity of the airways In addition, the close proximity of the $FEC_{1.0}$ values to the $FEC_{0.5}$ is also characteristic of the patients with pulmonary emphysema This figure was taken from data published elsewhere [81]

method of evaluating air flow characteristics of the lung Even though those measures are more directly a function of the dynamic mechanical properties of the lung, they, for the most part, require more complex equipment and the necessity for analysis of recorded tracings. The analysis of spirograms has been made more simple by the use of a sliding rule developed by Kory [95] More recently, Goldsmith[96, 97] has developed an effective and simple device for measuring peak expiratory flow rate, for which he has found an excellent correlation of +0 93 with the $FEC_{0.5}$. This apparatus has the disadvantage of not providing a measurement of volume.

No data are available for comparing these methods with direct mechanical function measurements or with other indirect technics Thus, for the doctor or clinic with minimal recording equipment, the simple vital capacity spirometers or meters with an appropriate mechanism for measuring specific timed segments of a *forced expiratory vital capacity* will provide a convenient and reliable means for evaluating these dynamic functions of ventilation.

The use of two time intervals, such as the first 0 5 and 1 0 second portion of a forced expiration, will supply the type of information obtained by the maximal mid-expiratory flow test, since patients with emphysema who exhibit expiratory airway collapse will demonstrate a marked reduction in flow rate during the second 0 5 second of expiration. This phenomenon is illustrated in FIGURE 16, which

further shows how this type obstruction differs from that seen in patients with bronchial asthma. Recognition of this special type of expiratory obstruction is important since it is responsible for the inordinate reduction of the effectiveness of such vital functions as coughing and exercise ventilatory capacity, wherein rapid forced breathing is necessary.

The analysis of maximal expiratory flow tracings, such as illustrated in FIGURE 16, is further enhanced by simultaneous measurement of the intraesophageal pressure so as to demonstrate the relationship between the flow rate and the transpulmonary pressure. This technic helps further to differentiate diffuse, large airway obstruction of the asthmatic type from the expiratory collapse type obstruction of small airways characteristic of emphysema. The peak of the expiratory flow curve, followed by a sharp reduction of flow, occurs at a relatively low transpulmonary pressure (R.P.) in those patients who exhibit other manifestations of pulmonary emphysema, whereas in patients with diffuse bronchitis or asthma, the transpulmonary pressure reaches a much higher pressure before the drop in air flow occurs. Presumably, decreased elastic support for the airway increases the tendency for the airway to

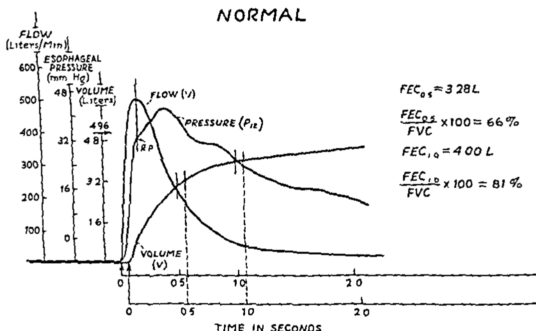
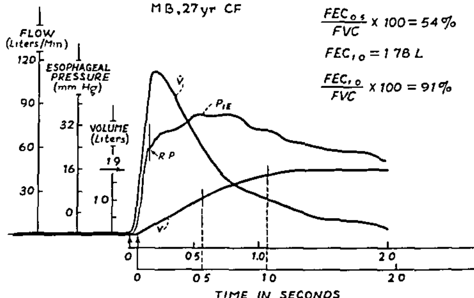


FIG 16—*Relationships of transpulmonary pressure to maximal expiratory flow rate and timed expiratory capacities* Simultaneous recordings of pneumotachographic flow curves, volume integral of flow and the transpulmonary pressure in (A) a normal subject, (B) a patient (W P) with pulmonary emphysema, and (C) a patient (M B) with bronchial asthma, both before and after the administration of a bronchodilator drug. The patients are the same as those whose data were demonstrated in FIGURE 15 Several aspects of the *instantaneous flow* curves are worthy of mention The sharp rise to a relatively high peak flow rate with equally as sharp a drop in flow rate to a low sustained flow under great force (high transpulmonary pressure) is characteristic of the mechanical alterations of pulmonary emphysema On the other hand, the relatively slower rise in flow rate to a lower peak which is, nevertheless, more sustained by a high transpulmonary pressure is typical of the changes noted in diffuse obstructive bronchitis or allergic asthma The esophageal or intrapleural pressure at the point of reversal of the flow peak (R P) corresponds to the ($P_T^{max\ eff}$), maximum effective intrathoracic pressure described by Campbell and co-workers [21] In both patients, the R P. at peak flow is higher after a bronchodilator drug was administered However, the most striking fact is the very low pressure at R P in the patient with pulmonary emphysema, demonstrating the effect of airway collapse resulting from small peripheral airway type of obstruction as contrasted with diffuse larger airway obstruction of a patient with asthma



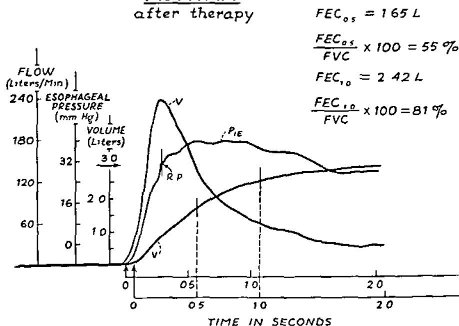
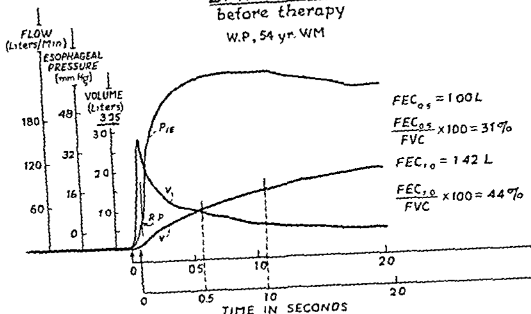


Fig. 16—(B)

collapse, and the sharp drop in flow rate to occur at lower transpulmonary pressures. The physical basis for these changes has been considered in a previous section. Campbell, Martin and Riley[21] have discussed in detail the theoretical aspects of similar observations.

In normal subjects the FEC_t bears a constant relationship to the FVC with very little age and sex variation.[95] Thus, in essence, a uniform relation exists between displaceable lung volume and the velocity of displacement. This is further emphasized by the demonstrable dependence of conductance on volume (Fig. 18). The mean value for the ratio 0.5



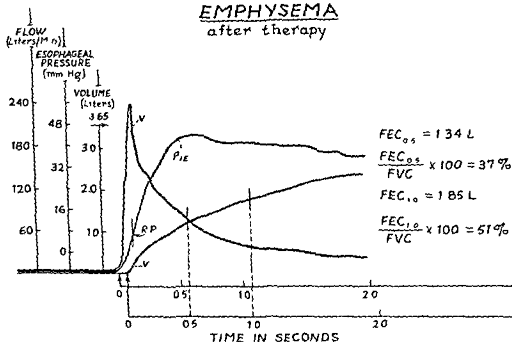
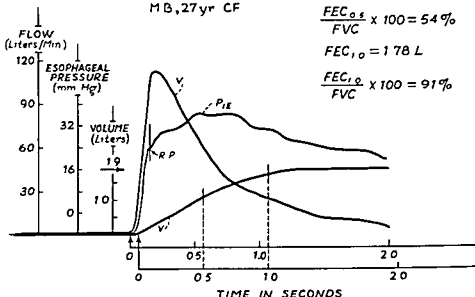


Fig 16—(C)

second forced expiratory capacity to the forced vital capacity, $FEC_{0.5} \times 100/FVC$, is 68 per cent, while $FEC_{0.75} \times 100/FVC$ is 77 per cent, and $FEC_{1.0} \times 100/FVC$ is 84 per cent

There is a small but significant age regres-

males. Pemberton and Flanagan,[99] as we Miller and Johnson,[98] found mean value this ratio in normal males over 40 yea age to be 79.1 ± 7.2 per cent and 80.3 ± per cent, respectively



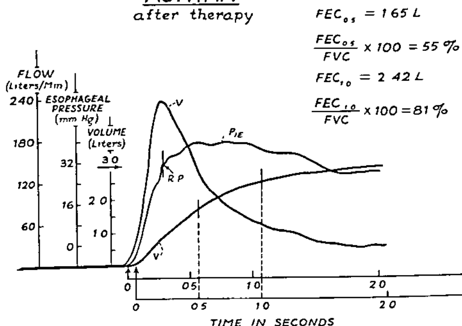


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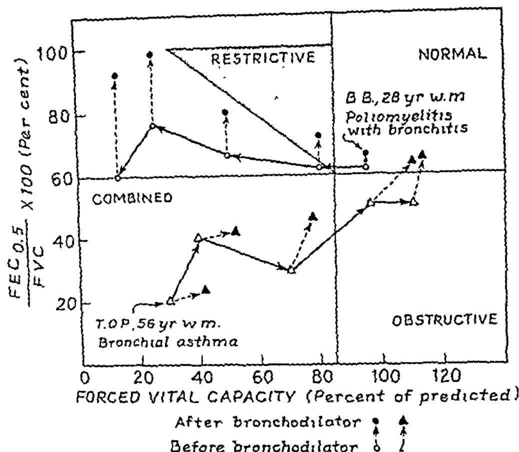


FIG 18.—*The nature of ventilatory disturbances as demonstrated by the quadrant plot* The quadrant plot shown is a graphic system for illustrating the character of ventilatory disturbances as they are observed in two patients during the course of their disease Values for the forced 0.5 second exp...

... tions, thus dividing the graph into four quadrants, identified as to the type of ventilatory disturbance that would be described by values appearing in any area of the graph The stippled area indicates a particular portion of the restrictive quadrant, where values are found for patients who lose displaceable lung volume without proportionate decrease in conductances, thus the FVC will be decreased to a greater extent ...

... point indicates a superimposed degree of airway obstruction not correctible by a bronchodilator drug or airway suctioning At this point, tracheostomy was performed The values plotted ... tions

Pro-

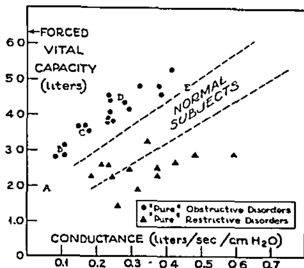


FIG 17—Vital capacity—conductance The relationship of conductance to changes in lung volume as reflected by the vital capacity The dashed lines define the limits of the data on normal subjects Patients with obstructive ventilatory disorders, shown as solid circles, reveal low compliances in proportion to their maximal displaceable lung volumes, while patients with restrictive ventilatory disorders show conductances that are, for the most part, high in proportion to the vital capacities One patient (M B, FIG 15) whose data are represented by the letters A through E was followed during the course of steroid treatment for asthma to demonstrate that the volume disturbance was characteristically corrected before the conductance increased commensurate with the increase in vital capacity This figure was taken from data published elsewhere [81]

values are a function of lung capacity in normal individuals (FIG. 17), any measure of air flow used as an index of airway resistance must be considered in the light of the displaceable lung volume The ratio of $FEC_t \times 100/FVC$ thus becomes a useful means of defining the characteristics of air flow in different individuals in terms of the displaceable lung volume.

On the basis of extensive experience with this relationship, it is apparent that the acceptable lower limit of normal for the $FEC_{0.5} \times 100/FVC$ is 60 per cent and for $FEC_{1.0} \times 100/FVC$ 75 per cent. When employed in this manner, FEC_t measurements become more meaningful expressions with respect to the function of each individual than if simply used as an estimate of the volume of air flow in terms of predicted values.

In order to illustrate graphically the utility of these indirect measures of mechanical function, a quadrant plot (FIG. 18) is presented In such a system, where the relationship between changes in the ratio air flow to volume, $FEC_t \times 100/FVC$, is plotted against volume (FVC) expressed as per cent of predicted,* the changing nature of ventilatory defects can be followed, either during the natural course of disease or as they are altered by treatment. The two cases shown in FIGURE 18 are illustrative of the possibilities. In such a graphic system a ventilatory defect exhibiting a normal volume displacement but a decreased velocity of displacement would appear in the obstructive quadrant. When volume displacement is decreased but the velocity of volume displacement is normal, the result would be described as a restricted ventilatory defect The stippled area of the restrictive quadrant requires additional comment Since purely restrictive disturbances, such as pleural fibrosis, pleural effusion and muscular weakness resulting either from disease or curare-like drugs, usually display a loss of available peripheral lung units without any significant alteration in the main airways, the FVC tends to be reduced to a greater extent than is the $FEC_{0.5}$ Accordingly, the $FEC_{0.5}$ will be a greater fraction of the FVC, reaching 100 per cent by the time the FVC is reduced to 30 per cent predicted. When both volume and velocity of volume displacement are decreased, the ventilatory disturbance is both obstructive and restrictive, or combined, in type

With regard to the changes in $FEC_t \times 100/FVC$, it must be emphasized that as a ratio it should not be considered an empirical figure, but rather interpreted with due consideration of the numerator and denominator separately.

Thus, the correlations demonstrated between the FEC_t and conductance, between the FVC and compliance, as well as other relationships presented, give real meaning to these estimates of mechanical function

* Normally, the FVC should be greater than 85 per cent of the predicted volume when taken from the nomogram derived from normal data obtained in this laboratory (FIG 19)

Values in normal subjects and in patients with respiratory disease. J. Clin Invest 35: 327, 1956
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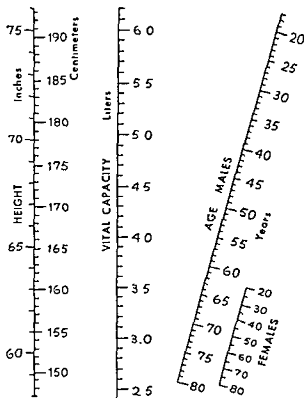


Fig 19.—Nomogram for prediction of normal vital capacities in both males and females: ages 17–80 years [98]

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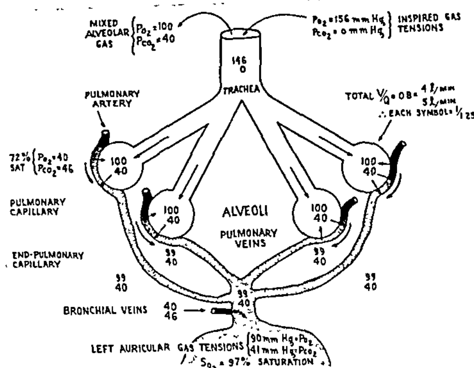


FIG 1 —Respiratory gas tensions in various parts of the lungs and the pulmonary circulation are depicted as they exist in a normal subject In each set of numbers, P_{O_2} is represented above and the P_{CO_2} below The S_{O_2} is the % O_2 saturation calculated from those gas tensions, assuming a normal O_2-Hb dissociation curve An A-a (alveolar arterial) P_{O_2} difference of 10 mm Hg and an A a P_{CO_2} difference of 1 mm Hg exists, assuming arterial gas tensions equal LA gas tensions Nine mm Hg of the A-a P_{O_2} difference results from 4% venous admixture through the bronchial veins, while 1 mm Hg difference represents the residual diffusion gradient across the alveolar-capillary membrane at the end of the pulmonary capillary

perfused However, methods for detecting this type of physiologic abnormality have been developed only in recent years and are, therefore, not generally appreciated

Localized Maldistribution

Many patients suffer the consequences of maldistribution of blood and gas in only part of the lungs because areas of disease are localized to a few segments or lobes of one lung. If these diseases are infectious or malignant in origin, then resection of the diseased areas may be advisable. However, in order to be sure that the remaining lung can fulfill the patient's needs for gas exchange before the diseased areas are removed, one would like to test the function of the lung tissue which would be left. Evaluation of such cases is best done by means of differential bronchospirometry. By means of a double-lumen tracheal catheter, ventilation and oxygen consumption of each lung can be measured separately. Detailed description of this technique and interpretation of the findings are available in the first edition of *Clinical Cardio-*

TABLE 1 —*Disturbances in the Distribution of Gas and Blood*

Ratio		Anatomic Abnormality → Physiologic Result
$\dot{V}_E/\dot{Q}_t \uparrow$	=	right-to-left shunts → venous admixture
$\dot{V}_E \uparrow /\dot{Q}_t$	=	expired-to-inspired shunts → excess dead space
mal $\dot{V}_A/\dot{Q}_c$	=	airway obstruction → nonuniform distribution of gas
$\dot{V}_A$/mal $\dot{Q}_c$	=	pulmonary capillary obstruction → nonuniform distribution of blood
$\dot{V}_E$	=	total ventilation.
$\dot{Q}_t$	=	total right heart output
$\dot{V}_A$	=	alveolar ventilation
$\dot{Q}_c$	=	pulmonary capillary flow.
mal	=	nonuniform distribution

Distribution of Gas and Blood in the Lungs

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EFFICIENT gas exchange within the lungs depends on five factors: (1) suitable inspired oxygen and carbon dioxide tensions, (2) a reasonably permeable alveolar capillary membrane, (3) adequate flow of gas and blood into and out of the lungs, (4) a relatively constant ratio of ventilation to perfusion throughout the lungs and (5) a high degree of uniformity of distribution of *both ventilation and perfusion*. The first three factors are discussed elsewhere in this book, leaving the last two factors to be discussed in this Chapter. These two factors both relate to distribution and will be considered in the following order: The many aberrations from normal that can occur in pulmonary disease will be discussed from a theoretical point of view, including the calculations for quantitating each defect in distribution, an experimental approach combining a number of methods simultaneously will be presented, clinical applications of these concepts and tests will be discussed.

Theoretical Discussion

Uniform distribution of inspired gas and venous blood in the lungs is depicted in Figure 1. Normal gas tension relationships are shown for comparison with the distorted relationships which are discussed later. In general, there are four basic defects in respiratory physiology related to the distribution of gas and blood in the lungs; many combinations and permutations of these may occur in pulmonary disease, but they can all be broken down and quantitated in terms of these four basic defects (Table 1). First of all, shunts of blood and gas, which represent two types of maldistribution, will be considered. In the first case, perfusion exceeds ventilation or blood by-passes alveoli altogether, resulting in what is called venous admixture. In the second case, ventilation exceeds perfusion, so that in effect some gas is never exposed to capillary blood, resulting in what is called dead space ventilation. These shunt situations are well discussed by Riley.[33] The third and fourth types of maldistribution are broken down into those in which there is not an excessive quantity of blood flow or ventilation but in which the quality of distribution of either blood or gas is distorted.

In Figure 2, complete maldistribution is illustrated, i.e., the ventilated but unperfused type of alveoli are represented on the left and the perfused but unventilated type of alveoli on the right. Martin and Young are approaching the disturbances of the ventilation-to-perfusion ratio in terms of their frequency distribution in the gamut from 0 to infinity.[26] However, it is technically difficult, if not impossible, at the present time to obtain the basic information to define precisely the number of alveoli operating at all the intermediate ratios. Briscoe[4] has approached the problem by relating inert gas washout curves to (A-a) P_{O_2} differences. This chapter describes our attempts to characterize the physiologic defects listed in Table 1 in various pulmonary diseases by using nitrogen washout, (A-a) P_{O_2} differences and (A-a) P_{CO_2} differences.

Figure 2 is a striking example of the importance of proportional distribution of gas and blood in the lungs. The situation presented is lethal, despite the fact that the quantity of ventilation and perfusion are both normal, because the diffusing capacity of the lungs would be zero: All of the ventilation would be physiologically equivalent to dead space ventilation and all of the blood leaving the lungs would be venous. The result would be an alveolar ventilation of zero and venous admixture of 100 per cent.

This same degree of maldistribution can occur at the microscopic level if alternate alveoli are not ventilated and the other alveoli are not

Categories of Maldistribution

Venous Admixture

Venous blood can enter the arterial stream in three ways (Fig. 3) (1) normal true shunts through thebesian and bronchial veins (B V.); (2) abnormal anatomic right-to-left shunts (A-V shunts) through pulmonary aneurysms or angiomata, congenital defects in the cardiac septa (A S D) or other central communications such as a patent ductus arteriosus, and (3) abnormal "virtual" shunts through pulmonary capillaries in poorly ventilated alveoli If alveolar ventilation is adequate to produce alveolar oxygen tensions of 100 mg Hg or more and there is no significant diffusion barrier across the alveolar capillary membrane, then any arterial unsaturation which exists must be due to one or more of the above-mentioned shunts Normally, one can assume that the oxygen tension at the end of a given pulmonary capillary will be within a mm Hg of that in its alveolus Therefore, knowing alveolar P_{O_2} and arterial P_{CO_2} or arterial pH one can calculate what the oxygen saturation of this end-capillary blood would be, assuming a normal O_2-Hb dissociation curve[21, 25] Finally, it may be useful to know the extent to which the peripheral O_2 saturation is lower than end-pulmonary capillary saturation (proportional to the amount of venous admixture), also, to know how this venous blood entered the arterial side of the circulation This can be approached as follows

Differentiation of shunts When the patient is breathing room air, venous blood passing through any of the routes enumerated above will contribute significantly to the depression of peripheral arterial oxygen saturation The contribution of "virtual shunts" can be minimized by having the patient breathe 40 per cent O_2 This is so because after 10 to 15 minutes this higher concentration will enter all patent and communicating alveoli unless they are very poorly ventilated, and will saturate the end-pulmonary capillary blood of each Conversely, because of the shape of the O_2-Hb dissociation curve, lowering the inspired O_2 concentration to 12 to 16 per cent minimizes the effect of venous admixture, through any channel, and permits evaluation of a diffusion barrier as a cause of arterial unsaturation. These problems will be discussed in greater detail in the following paragraphs

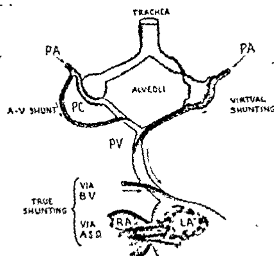


Fig 3 —Arteriovenous (A-V) communications are a "true" type of shunt, as are the bronchial veins (BV), thebesian veins, or septal defects "Virtual" shunting is physiologically important when many alveoli are obstructed and blood continues to flow through the pulmonary capillaries, anatomically speaking, these are not "true shunts" PA, pulmonary artery, PC, pulmonary capillary, PV, pulmonary vein, BV, bronchial vein, ASD, atrial septal defect, RA, right atrium, LA, left atrium

Cardiac output Until simple methods for determining cardiac output are more universally available, estimation often has to suffice If one is certain that there is no cardiac disease, then it is fairly safe to assume an A-V saturation difference of 20 per cent because an error of ±5 per cent will not affect the calculations appreciably However, when there is any sign of cor pulmonale or intrinsic heart disease, it is best to try to make allowances for this by assuming an appropriate A-V difference in saturation, e g , 15 per cent for cor pulmonale not in failure, 30 to 40 per cent when signs of failure are present, depending on their severity. Circulation time can be useful in trying to make these estimates if cardiac output cannot be measured; this is admittedly unsatisfactory and only a compromise solution to the problem.

One can then relate the drop of oxygen saturation from that calculated for end-pulmonary capillaries to that measured in a peripheral

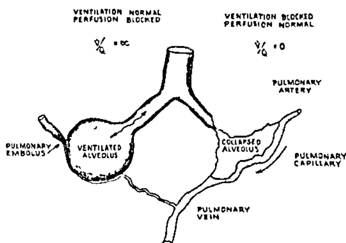


FIG 2—A pulmonary embolus prevents all blood flow on one side while collapse of the alveolus prevents all ventilation on the other As a result, the ventilation-to-perfusion ratio $\dot{V}/Q$ is infinite on the left and zero on the right

pulmonary Physiology as well as in many other books and journals[49, 18]

An interesting development in the last few years in combination with bronchospirometry has been the production of temporary unilateral pulmonary artery occlusion on the diseased side by the inflation of a balloon on the end of a cardiac catheter[19] In this way the conditions after resection of one lung can be accurately simulated in advance However, the ability of the pulmonary vascular bed of the good lung to accommodate the total blood flow after resection can be tested much more easily without pulmonary artery occlusion by exercising the patient to the point at which the blood flow through the good lung doubles Blood flow through the better lung can be assumed to have doubled when the rate of O_2 uptake by that lung has doubled, if the A-V difference for O_2 has remained constant

Temporary unilateral pulmonary artery occlusion is nevertheless the most accurate method for testing preoperatively the therapeutic indication for ligating a pulmonary arteriovenous aneurysm or for resection of localized pulmonary angiomata. Arterial unsaturation will clear completely with occlusion of one main branch of the pulmonary artery if aneurysms or other shunts in the lungs are limited to the side obstructed In this case, ligation should be seriously considered.

Diffuse Maldistribution

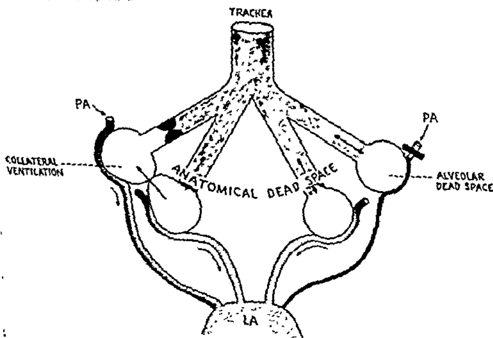
When the diseased areas are diffusely distributed throughout the lungs it is difficult to study the uninvolved, more normal areas separate from the diseased areas Special radiopaque bronchial catheters have been passed into segmental bronchi and bronchi of the third order by Martin et al.[25] The gas samples obtained by continuous suction through these catheters revealed somewhat higher ventilation-to-perfusion ratios in the apices as compared to the bases of the lungs in human beings. It has been further determined that this nonuniformity is due to reduced perfusion of the apices in the erect posture Efforts to sample gas through catheters directed into the bronchi of diseased areas of the lungs have been frustrated by aspiration of secretions instead of gas, in our laboratory. Martin reports successful gas sampling in diseased segments, however. Such discrete samples of gas or blood would be very sensitive indicators of localized disease in its early stages Until localized sampling is more practical, however, we will have to rely on mixed samples of blood, draining both healthy and diseased areas of the lungs, and mixed samples of alveolar gas ventilating all types of alveoli Since the healthy areas tend to compensate for the diseased areas it is remarkable that present methods are as sensitive as they are It is only because of the different physical-chemical characteristics of CO_2 and O_2 that certain calculations can be made, permitting estimation of the nonuniformity of distribution of blood and gas.[34] More specifically, it is the great solubility of CO_2 and the nonlinear nature of the oxygen-hemoglobin (O_2-Hb) dissociation curve that permit this differentiation

Virtual shunting. An alternate approach to venous admixture is to administer 40 per cent O_2, determine the arterial P_{O_2} and calculate the alveolar P_{O_2}. After 10 minutes of breathing 40 per cent O_2, all end-pulmonary capillary blood is probably saturated, even that leaving poorly ventilated alveoli, because of collateral ventilation (Fig. 5). The calculated venous admixture, therefore, would not include the virtual shunting from right to left, but only true, anatomic shunting. It is true that venous blood perfusing completely unventilated alveoli would still contribute to arterial unsaturation, but such alveoli usually collapse before long and perfusion ceases.[29] Blebs and bullae that do not communicate with the tracheobronchial tree will become oxygenated only very slowly. However, if the perfusion of such blebs is appreciable, the low total pressure of gases in venous blood will slowly absorb the "trapped" gas. Table 2 presents a calculation of the subatmospheric pressure of dissolved gases in venous blood. This table is based on the assumption that an alveolar-arterial gradient of 10 mm. Hg exists for P_{O_2} and that the subject is in a steady-state.

Table 2.—*Normal Gas Tensions*

	Alveolar mm. Hg	Arterial mm. Hg	Venous mm. Hg
P_{O_2}	100	90	40
P_{CO_2}	40	40	46
P_{H_2O}	47	47	47
P_{N_2}	573	573	573
Total pressure	760	750	706
Barometric pressure	760	760	760

The partial pressure of oxygen in blood traversing peripheral capillaries falls much more (50 mm. Hg) than the P_{CO_2} rises (6 mm. Hg), resulting in a total gas pressure in venous blood 44 mm. Hg below atmospheric or total alveolar pressure. The result is that gas in closed pockets in the lungs or elsewhere in the body is absorbed in proportion to the quantity of venous blood it is exposed to and the solubility of the gases in the blood.



...atom of the lungs is shaded to show the ana-... despite absence of ... ntilation, goes ... , as in the left-hand alveolus. LA, left atrium, ... tery.

artery, to the A-V difference in saturation thus

$$\frac{S_c' - S_a}{S_c' - S_v} = \frac{\dot{Q}_s}{\dot{Q}} = \% \text{ venous admixture} \qquad (1)$$

S_c' = saturation of end-pulmonary capillary blood

$S_{\bar{v}}$ = saturation of mixed venous blood

S_a = saturation of arterial blood.

$\dot{Q}_s$ = shunt in L./minute

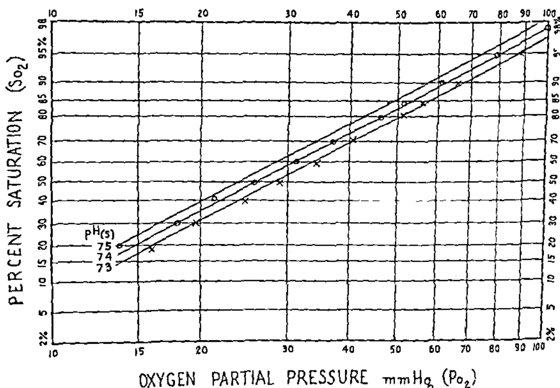
$\dot{Q}$ = total blood flow in L./minute.

For example, if S_a = 98 per cent and S_c' = 99 per cent and $S_{\bar{v}}$ = (S_a − 20) or 78 per cent then

$$\frac{99 - 98}{99 - 78} = \frac{1}{21} = 4.8\% \text{ venous admixture}$$

In order to calculate the O_2 saturation which would exist at a given P_{O_2} in the end-pulmonary capillary as accurately as possible, it is best to replot the O_2-Hb dissociation curve on log-probit paper so that it is approximately a straight line within the physiologic range [39, 50] Ideally, one would also like to have the pH value of the arterial blood so that the proper dissociation curve can be used (Fig. 4). Then one can use the arterial P_{O_2} and pH to calculate the following: (1) the per cent saturation for the arterial blood, (2) the per cent saturation of end-pulmonary capillary blood, assuming that end-capillary pH equals arterial pH and that end-pulmonary capillary blood P_{O_2} equals calculated alveolar P_{O_2}, and (3) the estimated per cent saturation of mixed venous blood

Diffusion effect. If, for some reason, a diffusion block is suspected, one could administer 12 to 16 per cent O_2 and repeat the collection of arterial blood and expired gas in order to measure the diffusing capacity for O_2 [37] Then, according to Riley's "trial and error" procedure, one could determine how much the diffusion barrier may be contributing to the drop of O_2 tension from the mean "effective" alveolar value to the end-pulmonary capillary value. In this way, one can correct the end-pulmonary capillary saturation value for any diffusion barrier and carry out the calculation of venous admixture with greater accuracy



anatomic dead space (V_D *anat.*) and alveolar dead space (V_D *alv.*):

$$V_D\ physiol. = V_D\ anat + V_D\ alv$$

Pappenheimer introduced the terms "parallel" and "series" in order to systematize concepts of dead space. He designates alveoli which are ventilated but not perfused as "parallel dead space," because they are ventilated in parallel with other alveoli; and the tracheobronchial tree as "series dead space," because these spaces are ventilated in series with alveoli.[19] Blocked alveoli present a problem to this approach because they may be ventilated through "alveolar pores," making the contiguous alveoli which are patent, function as dead space (as in the alveoli on the left in FIGURE 5). Some years ago these pores were studied physiologically by Lindskog[20] and were described pathologically by Macklin.[21] More recently, McLean has developed a theory of the pathogenesis of emphysema through overinflation of great numbers of obstructed alveoli by collateral ventilation.[22] However, for the purposes of this discussion no attempt will be made to quantitate transalveolar or collateral ventilation.

The actual calculation of dead space can be reasoned out as follows: If the alveoli were right at the lips, so that there was no anatomic dead space, then alveolar CO_2 would equal the mixed expired CO_2 in a bag of expired air because there would not be any dilution of alveolar CO_2 with dead space air. Therefore, the anatomic dead space is proportionately greater as the discrepancy between alveolar CO_2 ($P_{A_{CO_2}}$) and mixed expired CO_2 ($P_{E_{CO_2}}$) increases. In fact, the ratio of (alveolar-expired/alveolar) is the portion of the tidal volume (V_T) which does not participate in gas exchange, and is expressed by the Bohr equation:

$$V_D\ anal. = \left(\frac{P_{A_{CO_2}} - P_{E_{CO_2}}}{P_{A_{CO_2}}}\right) V_T \qquad (5)$$

assuming that the inspired CO_2 concentration is negligible.

If there are areas of the lungs which are being ventilated, but not perfused, the alveolar P_{CO_2} in these alveoli will be very low because no CO_2 can be delivered to them by the venous blood (FIG. 6). Therefore, unperfused alveoli will have only end-tidal alveolar CO_2 inhaled from the tracheobronchial tree, diluted by inspired air. When gas from unperfused alveoli mixes

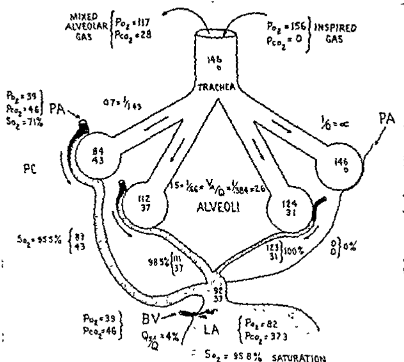


FIG. 6.—Respiratory gas tensions are designated as P_{O_2} above and P_{CO_2} below, calculated on the basis of $\dot{V}/\dot{Q}$ ratios of 0.7, 1.5, 2.6 and infinity. A-a P_{O_2} difference of 35 mm Hg and A-a P_{CO_2} difference of 9 mm Hg result from the maldistribution of blood flow. Ten mm Hg of the A-a P_{O_2} difference is due to 4 per cent venous admixture through the bronchial veins.

Anatomic shunting. The calculation of shunting when the patient is breathing higher oxygen concentrations than atmospheric can be done as described by Berggren.[3] The amperometric method of Berggren is ideal for determination of arterial P_{O_2} when the oxygen tension exceeds 100 to 120 mm Hg because the bubble-equilibration method of Riley is not applicable in this range without repeated analyses. However, in order to calculate the portion of cardiac output perfusing unventilated alveoli during high-oxygen breathing, oxygen saturation no longer can be used because the hemoglobin is 100 per cent saturated. Therefore, the dissolved oxygen or P_{O_2} is used for the calculation, assuming an A-V difference in O_2 content of 5 vol. per cent. The solubility of O_2 is taken to be 0.3 vol. per 100 mm. Hg P_{O_2} or the O_2 content of plasma = 0.003 vol. per cent × P_{O_2} of plasma. Therefore,

$$\dot{Q}_s/\dot{Q} = \frac{0.003\ (P_{A_{O_2}} - Pa_{O_2})}{0.003\ (P_{A_{O_2}} - Pa_{O_2}) + 5\ vol\ \%)} \quad (2)$$

and, since $\frac{5\ \text{vol.}\ \%}{0.003\ \text{vol}\ \%} = 167$

$$\text{Then } \dot{Q}_s/\dot{Q} = \frac{P_{A_{O_2}} - Pa_{O_2}}{(P_{A_{O_2}} - Pa_{O_2}) + 167} \quad (3)$$

in which $P_{A_{O_2}}$ = alveolar O_2 tension, Pa_{O_2} = arterial O_2 tension, and O_2 sol = O_2 solubility.

For example, if the patient is breathing 100 per cent O_2 and P_B = 760 mm Hg then in the normal alveoli P_{H_2O} = 47 mm. Hg, P_{CO_2} = 40 mm Hg and P_{O_2} = 672 mm. Hg. If arterial P_{O_2} = 662 mm Hg, then:

$$\dot{Q}/Q = \frac{(672 - 662)}{(672 - 662) + 167} = \frac{10}{10 + 167} = 5.7\%$$

If a patient has such poor alveolar ventilation that the mean "effective" alveolar P_{O_2} is low (less than 80 mm Hg), then the end-pulmonary capillary blood oxygen saturation will not fall on the flat portion of the O_2-Hb dissociation curve (e.g., 95 to 100 per cent saturation) plotted on linear coordinates. Furthermore, the saturation will be even lower, at a given O_2 tension, when there is hypercapnea, because the affinity of hemoglobin for oxygen decreases as pH falls

block effect when the subject breathes roo
and it would not be safe to give lower
atmospheric oxygen concentration to te
impeded diffusion. Although venous admi
can be evaluated in these cases by raisin
veolar P_{O_2} to the normal range by administ
30 per cent O_2, it is necessary to use a ca
monoxide method to test diffusing capaci
a situation like this. If the steady-state me
of Filley[13] is used, the diffusing capacity o
lungs for carbon monoxide ($D_{L_{CO}}$) can be
verted into $D_{L_{O_2}}$ as a first order approxim
in multiplying by the factor 1.23. (This f
relates the solubility and molecular weig
the two gases.) Then the gradient from
olar P_{O_2} to mean pulmonary capillary b
P_{O_2} can be calculated from the $D_{L_{CO}}$ and
alveolar-end capillary gradient derived. In
way, one can correct the calculated venous
mixture for any diffusion impediment.

The calculation of the "effective" mea
veolar P_{O_2} is, at any level of O_2 breathing, b
on the alveolar air equation is

$$P_{A_{O_2}} = P_{I_{O_2}} - Pa_{CO_2}\left[F_{I_{O_2}} + \frac{1 - F_{I_{O_2}}}{R_E}\right]$$

It requires only that the following data
known: inspired oxygen tension ($P_{I_{O_2}}$) and
centration ($F_{I_{O_2}}$), respiratory exchange r
R_E = (CO_2 production/O_2 consumption) and
terial CO_2 tension (Pa_{CO_2}). The result is m
simply determined graphically, however,
a method devised by Rahn and Fenn
available in a very useful monograph form

Dead Space

First of all, it would seem best to define
various types of dead space which may deve
from maldistribution of blood or inspired
(Fig. 5). As one studies patients with disea
lungs, one finds a considerable number of ca
with abnormally large dead space. Such d
space is usually total "physiologic dead spa
(the volume of the tracheobronchial tree add
to the "alveolar dead space" resulting fr
the nonuniform distribution of blood and
in the lungs). In Figure 5 it can be seen t
the absence of blood flow to the alveolus at t
far right prohibits gas exchange in it, making
effective "alveolar dead space." Physiolo
dead space (V_D *physiol.*) is defined as includi

Finally, it should be noted that the perfusion of unventilated alveoli causes some increase in in end-tidal (alveolar-arterial) P_{CO_2} differences, but only one-third to one-fifth as much as the ventilation of unperfused alveoli. This is best appreciated in a nomogram by Severinghaus.[47]

Nonuniform Distribution of Inspired Gas

When inspired gas is not uniformly distributed to all parts of the lungs, this may be detected clinically in many ways, but can be quantitated only in physiologic terms. Clinical signs include diminished or absent breath sounds in poorly ventilated areas, whereas "brightening up" of overventilated areas may be observed during fluoroscopy. During open-chest surgery the unequal ventilation of various parts of the lungs is most apparent.

Nonuniformity of distribution of inspired gas, as illustrated in FIGURE 7, can be quantitated in a number of ways. The one which does not require expensive electronic physical-chemical gas analyzers is the "index of alveolar gas mixing." This is not actually an index of gas mixing in the alveoli but, rather, an index of maldistribution of inspired gas. It was devised by Cournand and his associates in 1941.[8] It consists simply of having the subject breathe 100 per cent O_2 for seven minutes and obtaining a forced alveolar sample for analysis at the end of this time (FIG. 8) This sample was analyzed for O_2 and CO_2 in the Van Slyke apparatus originally, now but is analyzed in a Lilly-type nitrogen meter in many laboratories In either case the alveolar N_2 has been found empirically to be less than 2 5 per cent after seven minutes breathing O_2 unless there is significant maldistribution of inspired gas.

Many attempts have been made to use the washout pattern, as recorded from breath to breath by a nitrogen analyzer. Plotting it on semilogarithmic paper, one may calculate the relative size of the compartments of the lungs which are emptying at various rates. The results of such calculations have been of theoretical interest but are not considered particularly useful for clinical purposes. It is important to note, however, that the rate of nitrogen washout is a function of alveolar ventilation and functional residual volume, as well as the uniformity of distribution. Probably the best corrections devised as yet are those of Fowler.[17]

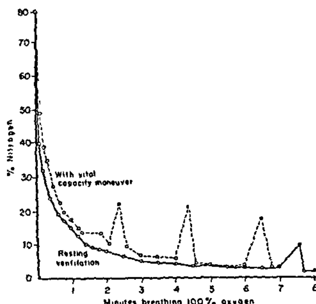


FIG 8 —The sharp peaks of nitrogen which can be produced by forced expiration at any point in a relatively normal nitrogen washout curve are characteristic of bronchiectasis. Vital capacity = (•). Numbers along the vertical axis indicate % nitrogen

In most cases it does not seem to be necessary to make corrections for alveolar ventilation and residual volume because, by seven minutes, even hypoventilated lungs have reached an alveolar nitrogen concentration less than 2 5 per cent (FIG. 8). However, there are undoubtedly patients with pulmonary disease in whom there is a mild degree of hypoventilation and increased residual volume in addition to maldistribution; these defects would result in a higher seven-minute alveolar N_2 than the same patient would have with adequate ventilation or if the residual volume were normal. In such cases the "single-breath test" offers an advantage over the nitrogen washout curve because it is less dependent on the depth of breathing and the residual volume.[7]

In the single breath test, alveolar ventilation and residual volume influence chiefly the absolute level of nitrogen resulting from a deep inspiration of 100 per cent O_2. It is the *rate* of increase of the alveolar nitrogen during expiration which is almost purely a function of the uniformity with which the inspired oxygen was

with gas from perfused alveoli, the mean alveolar P_{CO_2} is lowered considerably. The resulting (arterial-alveolar) CO_2 difference is not, of course, due to a true diffusion gradient for CO_2 across the alveolar capillary membrane but uneven distribution of blood [43] Furthermore, CO_2 is too highly soluble to permit a true gradient of any magnitude to develop, nor can it be due to venous admixture, because the A-V P_{CO_2} difference is only 6 to 9 mm Hg It has been pointed out by Severinghaus that this end-tidal alveolar-arterial CO_2 difference is proportional to the extent that there is ventilation without perfusion.[47] In order to quantitate this, he suggests the following calculation:

$$\left.\begin{matrix}\%\ \textit{alveoli ventilated}\\ \textit{but not perfused}\end{matrix}\right\} = \left(\frac{Pa_{CO_2} - P_{A_{CO_2}}}{Pa_{CO_2}}\right) \times 100 \quad (6)$$

e.g. if arterial CO_2 = 37 mm. Hg and alveolar CO_2 = 28 mm Hg then:

$$= \frac{37 - 28}{37} = \frac{9}{37} = 25\%$$

The volume of gas wasted on such unperfused alveoli can be calculated in this way

$$V_D \textit{ alveolar} = \left(\frac{Pa_{CO_2} - P_{A_{CO_2}}}{Pa_{CO_2}}\right) V_T \quad (7)$$

in which V_T = tidal volume

The most difficult part of this measurement is the determination of the end-tidal alveolar CO_2 when there is maldistribution of inspired gas as well as blood flow An infrared CO_2 analyzer (Liston-Beckman) is the best instrument for the determination of end-tidal alveolar CO_2 as distinct from dead space and midexpiratory alveolar CO_2.[40] Despite the fast response of this instrument there remains considerable difficulty in obtaining meaningful alveolar gas samples It is apparent from FIGURE 7 that in this case many poorly ventilated alveoli may not be represented in the end-tidal alveolar gas sample unless a forced expiration is made Even then some alveoli may not empty and the arterial P_{CO_2} will exceed the end-tidal alveolar P_{CO_2} sampled at the lips or nares Under these circumstances any persisting end-tidal (alveolar-arterial) P_{CO_2} difference must surely be due to ventilated but not perfused alveoli because use of the terminal alveolar CO_2 after forced expiration yields a higher reading than the mean alveolar CO_2 [11]

A calomel cell glass electrode for the determination of pH and P_{CO_2} directly in blood is the most accurate method for the determination of arterial P_{CO_2} [2, 21]

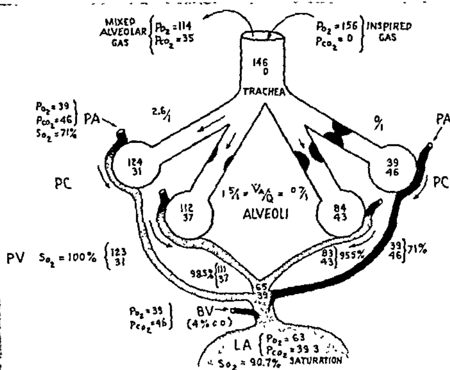


FIG 7 —Respiratory gas tensions designated are those which would develop if the distribution of blood flow were uniform and $\dot{V}/\dot{Q}$ ratios of 0, 0 7, 1.5 and 2 6 result because of nonuniform distribution of ventilation. An A-a P_{O_2} difference of 51 mm Hg and an A-a P_{CO_2} difference of 4 mm Hg result Only 2 mm. Hg of the A-a P_{O_2} is due to 4 per cent venous admixture through the bronchial veins

Finally, it should be noted that the perfusion of unventilated alveoli causes some increase in in end-tidal (alveolar-arterial) P_{CO_2} *differences*, but only one-third to one-fifth as much as the ventilation of unperfused alveoli. This is best appreciated in a nomogram by Severinghaus.[47]

Nonuniform Distribution of Inspired Gas

When inspired gas is not uniformly distributed to all parts of the lungs, this may be detected clinically in many ways, but can be quantitated only in physiologic terms Clinical signs include diminished or absent breath sounds in poorly ventilated areas, whereas "brightening up" of overventilated areas may be observed during fluoroscopy During open-chest surgery the unequal ventilation of various parts of the lungs is most apparent.

Nonuniformity of distribution of inspired gas, as illustrated in FIGURE 7, can be quantitated in a number of ways The one which does not require expensive electronic physical-chemical gas analyzers is the "index of alveolar gas mixing" This is not actually an index of gas mixing in the alveoli but, rather, an index of maldistribution of inspired gas It was devised by Cournand and his associates in 1941.[8] It consists simply of having the subject breathe 100 per cent O_2 for seven minutes and obtaining a forced alveolar sample for analysis at the end of this time (FIG 8) This sample was analyzed for O_2 and CO_2 in the Van Slyke apparatus originally, now but is analyzed in a Lilly-type nitrogen meter in many laboratories In either case the alveolar N_2 has been found empirically to be less than 2 5 per cent after seven minutes breathing O_2 unless there is significant maldistribution of inspired gas.

Many attempts have been made to use the washout pattern, as recorded from breath to breath by a nitrogen analyzer Plotting it on semilogarithmic paper, one may calculate the relative size of the compartments of the lungs which are emptying at various rates. The results of such calculations have been of theoretical interest but are not considered particularly useful for clinical purposes It is important to note, however, that the rate of nitrogen washout is a function of alveolar ventilation and functional residual volume, as well as the uni-

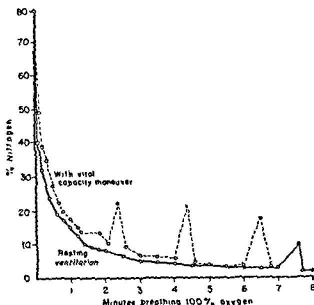


FIG 8.—The sharp peaks of nitrogen which can be produced by forced expiration at any point in a relatively normal nitrogen washout curve are characteristic of bronchiectasis Vital capacity = (•) Numbers along the vertical axis indicate % nitrogen

formity of distribution. Probably the best corrections devised as yet are those of Fowler[17]

In most cases it does not seem to be necessary to make corrections for alveolar ventilation and residual volume because, by seven minutes, even hypoventilated lungs have reached an alveolar nitrogen concentration less than 2.5 per cent (FIG 8) However, there are undoubtedly patients with pulmonary disease in whom there is a mild degree of hypoventilation and increased residual volume in addition to maldistribution, these defects would result in a higher seven-minute alveolar N_2 than the same patient would have with adequate ventilation or if the residual volume were normal. In such cases the "single-breath test" offers an advantage over the nitrogen washout curve because it is less dependent on the depth of breathing and the residual volume.[7]

In the single breath test, alveolar ventilation and residual volume influence chiefly the absolute level of nitrogen resulting from a deep inspiration of 100 per cent O_2. It is the *rate* of increase of the alveolar nitrogen during expiration which is almost purely a function of the uniformity with which the inspired oxygen was

with gas from perfused alveoli, the mean alveolar P_{CO_2} is lowered considerably. The resulting (arterial-alveolar) CO_2 difference is not, of course, due to a true diffusion gradient for CO_2 across the alveolar capillary membrane but uneven distribution of blood.[43] Furthermore, CO_2 is too highly soluble to permit a true gradient of any magnitude to develop, nor can it be due to venous admixture, because the A-V P_{CO_2} difference is only 6 to 9 mm Hg It has been pointed out by Severinghaus that this end-tidal alveolar-arterial CO_2 difference is proportional to the extent that there is ventilation without perfusion [47] In order to quantitate this, he suggests the following calculation.

$$\left.\begin{matrix}\textit{\% alveoli ventilated}\\ \textit{but not perfused}\end{matrix}\right\} = \left(\frac{Pa_{CO_2} - P_{ACO_2}}{Pa_{CO_2}}\right) \times 100 \quad (6)$$

e.g if arterial CO_2 = 37 mm Hg and alveolar CO_2 = 28 mm Hg then·

$$= \frac{37 - 28}{37} = \frac{9}{37} = 25\%$$

The volume of gas wasted on such unperfused alveoli can be calculated in this way

$$V_D \textit{ alveolar} = \left(\frac{Pa_{CO_2} - P_{ACO_2}}{Pa_{CO_2}}\right) V_T \quad (7)$$

in which V_T = tidal volume.

The most difficult part of this measurement is the determination of the end-tidal alveolar CO_2 when there is maldistribution of inspired gas as well as blood flow. An infrared CO_2 analyzer (Liston-Beckman) is the best instrument for the determination of end-tidal alveolar CO_2 as distinct from dead space and midexpiratory alveolar CO_2 [40] Despite the fast response of this instrument there remains considerable difficulty in obtaining meaningful alveolar gas samples. It is apparent from FIGURE 7 that in this case many poorly ventilated alveoli may not be represented in the end-tidal alveolar gas sample unless a forced expiration is made Even then some alveoli may not empty and the arterial P_{CO_2} will exceed the end-tidal alveolar P_{CO_2} sampled at the lips or nares. Under these circumstances any persisting end-tidal (alveolar-arterial) P_{CO_2} difference must surely be due to ventilated but not perfused alveoli because use of the terminal alveolar CO_2 after forced expiration yields a higher reading than the mean alveolar CO_2 [41]

A calomel cell glass electrode for the determination of pH and P_{CO_2} directly in blood is the most accurate method for the determination of arterial P_{CO_2}.[2, 21]

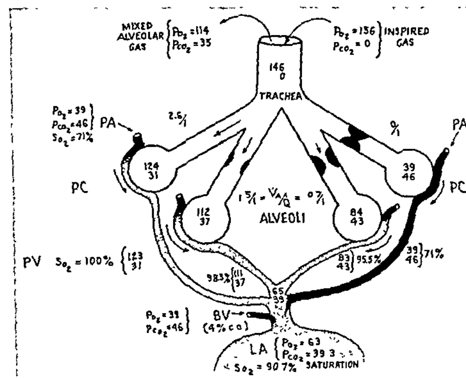


FIG 7 —Respiratory gas tensions designated are those which would develop if the distribution of blood flow were uniform and V/Q ratios of 0, 0 7, 1 5 and 2 6 result because of nonuniform distribution of ventilation An A-a P_{O_2} difference of 51 mm Hg and an A-a P_{CO_2} difference of 4 mm Hg result Only 2 mm Hg of the A-a P_{O_2} is due to 4 per cent venous admixture through the bronchial veins

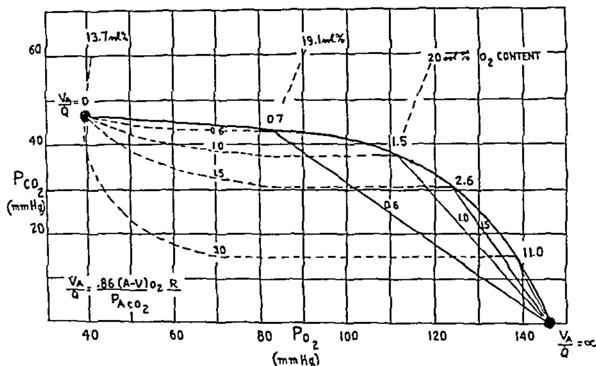


FIG 9—Assuming inspired gas tensions of P_{O_2} = 146 and P_{CO_2} = 0 and mixed venous blood gas tensions of P_{O_2} = 39, and P_{CO_2} = 46, the heavy black line between these points represents all the possible combinations of gas tensions in end-pulmonary capillary blood It is constructed by determining where the R Q for blood (horizontal dotted lines) intersects the R Q for expired gas (diagonal solid lines) The $\dot{V}_A/Q$ ratios ranging from 0 to infinity, for each alveolar or end-pulmonary capillary sample can be located along the solid curve if one gas tension is known The dashed diagonal lines above the curve indicate oxygen content in volumes per cent at different gas tension combinations, assuming an oxygen capacity of 20 ml /100 ml blood The dot at P_{O_2} = 115 mm Hg and P_{CO_2} = 36 mm Hg represents mean alveolar gas such as was produced in FIGURE 7; the alveoli having $\dot{V}/\dot{Q}$ ratios of 0 7, 1 5 and 2 6 are represented on the heavy line and correspond with the gas tensions in the appropriate alveoli in FIGURES 6 AND 7

results chiefly from the continuing ventilation of poorly perfused alveoli as discussed previously under "alveolar" dead space. There is a small effect from maldistribution of inspired gas, but the effect is only a fraction of that of unevenly distributed blood.[67]

The converse situation, i e , perfusion of unventilated alveoli, is quite likely to coexist when there is maldistribution of pulmonary blood flow. This phenomenon is discussed above under venous admixture. However, another method of calculation, analogous to that for ventilated but unperfused alveoli, has been suggested by Severinghaus.[67] He calls it the "per cent alveoli not ventilated," and it is calculated as follows:

$$\% \text{ A-a}P_{O_2} \text{ difference} = \frac{(P_{A_{O_2}} - Pa_{O_2}) \times 100}{P_{A_{O_2}}} \quad (8)$$

Then, by use of a nomogram especially constructed to fit a specific set of data, he calculates the "per cent alveoli not ventilated."

It seems that one might design a formula which would permit calculation of the "per cent alveoli not ventilated" more accurately under all conditions. This formula would merely correct the total (A-a) P_{O_2} difference for that portion of it which is due to anatomic or true R → L shunting, and true diffusion gradient. The true shunting effect on (A-a) P_{O_2} would have to be derived from measurement of the (A-a) P_{O_2} difference, breathing 40 per cent O_2 and corrected to its equivalent when

distributed The factors which influence this slope significantly are the inspiratory volume, end-inspiratory pause and expiratory flow rate.[22] However, they are relatively unimportant in comparison to maldistribution of inspired gas and can be minimized by holding them as constant as possible, e.g., 1 liter inspiratory volume, no end-inspiratory pause and an expiratory flow rate of 30 to 50 L/min

The technic for measuring single-breath N_2 slopes can be done most simply by attaching a low-torque potentiometer to the wheel of a spirometer so that, as it rotates, it serves as a variable voltage divider across a 1.5 volt dry cell.* In this way the volume and rate of alveolar N_2 can be amplified and recorded simultaneously

The most complete review of the intrapulmonary distribution of inspired gas in recent years is that compiled by Fowler.[16] In it, he presents the evidence for mild, nonuniform ventilation in young adult subjects without recognizable pulmonary disease

Inert gas clearance studies, as with N_2 or He, are almost completely insensitive to disturbances in the distribution of pulmonary blood flow and the rate of pulmonary blood flow. Fortunately, the rate of nitrogen elimination from the pulmonary capillary blood is infinitesimal compared to the rate of clearance from the alveoli.

On the other hand, the slope of alveolar CO_2 during expiration is very much affected by the rate of pulmonary blood flow Of course, alveolar CO_2 is also inversely proportional to alveolar ventilation. Therefore, the rate of change of alveolar CO_2 during expiration is a function of the $\dot{V}a/\dot{Q}c$ ratios existing in the lungs.[11]

Knowing the inspired gas tensions and the mixed venous gas tensions, and assuming a steady-state in which the respiratory exchange ratio (R_E = R.Q for expired gas) equals the blood respiratory gas ratio (R_b = R.Q for blood), one can make some interesting calculations using the O_2-CO_2 diagrams of Rahn and Fenn.[32] First, one can construct a curve along which all possible $\dot{V}/\dot{Q}$ ratios must lie (Fig 9). Then, assuming that each sample of alveolar P_{CO_2} reflects some pulmonary capillary P_{CO_2}, one can calculate the severity of maldistribution in terms of the range of $\dot{V}/\dot{Q}$ ratios about the mean value determined from mixed alveolar gas and mixed arterial blood This method will underestimate, if anything, the maldistribution of blood in relation to gas because alveolar gas samples with very low CO_2 mix with samples of gas with higher CO_2 concentration in the tracheobronchial tree during expiration Those alveoli which are obstructed, and therefore not ventilated, are not even represented, if they are perfused, the blood will be accounted for as venous admixture. Gas pockets, cysts or bullae which do not communicate with the tracheobronchial tree during resting ventilation can best be detected by the body plethysmographic method of Dubois for total thoracic gas volume.[10]

* Warren Collins Company, 555 Huntington Ave, Boston, Massachusetts

Nonuniform Distribution of Blood Flow

It is entirely possible for a patient to be experiencing significant dyspnea and yet have practically normal ventilatory tests, normal distribution of inspired gas, normal diffusion capacity at rest and a normal amount of venous admixture The distribution of blood in the lungs can be uneven, as in FIGURE 6, and yet all these tests can be within normal limits The most striking example of this is the patient with fresh pulmonary emboli, before infarction has altered gas distribution.[35] The dyspnea is presumed to be due to acute pulmonary hypertension and decreased compliance[42] more than to inefficient gas exchange

Routine tests in most laboratories do not detect nonuniform distribution of blood flow as such, unless some investigator is particularly interested in it and is, therefore, measuring alveolar CO_2 and arterial CO_2 simultaneously. In the presence of pulmonary embolism, an abnormal gap develops between these values. If the arterial CO_2 were located in relation to the V/Q ratio curve mentioned above, this abnormality would also be apparent The difference between end-tidal alveolar CO_2 and arterial CO_2

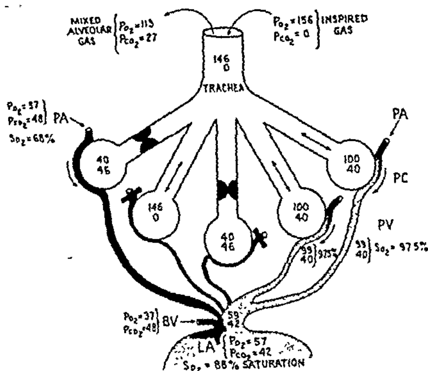


FIG 10.—Respiratory gas tensions which would result from maldistribution of both ventilation and blood flow are represented here. Two out of five, or forty per cent of alveoli are blocked and 40 per cent of pulmonary capillaries are obliterated or clotted. An A-a P_{O_2} difference of 56 mm Hg and an A-a P_{CO_2} difference of 15 mm Hg developed under these circumstances. Only 2 mm Hg of the A-a P_{O_2} difference is due to 4 per cent venous admixture. The $\dot{V}/\dot{Q}$ ratios in this case range from 1.3 in the two normal alveolo-capillary units to infinity in the unit which is ventilated but not perfused. These $\dot{V}/\dot{Q}$ ratios can be located on the solid curve in Figure 9 by use of successive discrete infrared CO_2 analyzer readings.

attributed to actual alteration in the nature of the alveolar capillary membrane. This type of correction for maldistribution is only an approximation, but should help delineate the actual causes of impaired diffusion.

Protocol

Ideally, one would like to have a simple method available for measuring each of these variables simultaneously, inconveniencing the patient as little as possible. An experimental approach has been evolved in our laboratory which, by means of a number of simultaneous measurements, permits evaluation of the most important factors in distribution. However, it is expensive, somewhat complicated, and still requires arterial sampling. It consists of recording simultaneously expired gas volume, alveolar N_2 and alveolar CO_2 during forced expiration, and after a deep breath of 100 per cent O_2. Arterial blood and mixed expired gas are sampled simultaneously while the subject breathes room air in a steady-state before breathing O_2 and again after 10 minutes of O_2 breathing. With these three procedures, one can measure all aspects of maldistribution of gas and blood discussed here in about 20 minutes.

Such an arrangement permits evaluation of the distribution of gas (N_2 slope), distribution of blood (alveolar-arterial P_{CO_2} difference), uniformity of $\dot{V}/\dot{Q}$ ratios (alveolar CO_2 slope), dead space (anatomic and physiologic) and estimates of venous admixture (anatomic and physiologic).

Methods of Gas Analysis

The analyses of blood gas tensions must be carried out with the highest degree of accuracy possible, because otherwise the calculated distribution defects will be grossly in error. More specifically, the following methods are preferable: (1) arterial P_{CO_2} determined with a glass electrode,[7, 21] and (2) arterial P_{O_2} determined with a Clark type of polarographic electrode, using the amperometric method. Ideally, one should also have further information: an accurate measurement of arterial pH. This permits one to correct the measured P_{O_2} to that which would exist at 7.40. A device for electrometric measurement of P_{CO_2} and P_{O_2} in the arterial blood was designed by Severinghaus and became commercially available during 1959.[46] The time-tested and less expensive, though tedious and less accurate method for determining

the subject is breathing room air. The formula would be:

$$\text{Total } (A\text{-}a)\,P_{O_2} \text{ difference} = \underbrace{(A\text{-}a)\,P_{O_2}}_{\text{due to true shunts}} + \underbrace{(A\text{-}a)\,P_{O_2}}_{\text{due to virtual shunts}} + \underbrace{(A\text{-}a)\,P_{O_2}}_{\text{due to diffusion barrier}} \quad (9)$$

$$\text{and \% Alveoli not ventilated} = \left[\frac{(A\text{-}a)\,P_{O_2} \text{ due to virtual shunts}}{\text{mixed alveolar } P_{O_2}}\right] \times 100 \quad (10)$$

$$\text{or \% Alveoli not ventilated} = \frac{[\text{total } (A\text{-}a)\,P_{O_2} - [(A\text{-}a)\,P_{O_2} \text{ true shunts} + (A\text{-}a\,P_{O_2} \text{ diffusion}] \times 100}{\text{mixed alveolar } P_{O_2}} \quad (11)$$

$$\text{\% Alveoli perfused but not ventilated} = \frac{51 - (2 + 1)}{114} = \frac{48}{114} = 42\% \quad (12)$$

This calculation measures the portions of the lungs which are perfused but unventilated, resulting in "virtual shunting" (Fig 3) If there is neither perfusion nor ventilation, then completely nonfunctioning alveoli can only be detected by body plethysmograph[10] One may conclude that with maldistribution of blood flow, both "alveolar dead space" and "venous admixture" are likely to occur, and each can be quantitated by the appropriate calculations

Diffusion Correction

It may be useful to calculate maldistribution in terms of the per cent alveoli not ventilated and per cent alveoli not perfused because the results permit approximation of the maximum diffusing capacity to be expected if the alveolar capillary membrane were completely normal As was seen in FIGURE 2, there cannot be any diffusion at the alveolar-capillary membrane unless gas and blood are moving on both sides of the membrane In other words, diffusing capacity is reduced in direct proportion to the reduction of area of interphase between blood and gas in the lungs. For instance, if 42 per cent of the alveoli are perfused but not ventilated, as in FIGURE 7, then the maximum diffusing capacity during exercise is reduced by 42 per cent. The *resting* diffusing capacity may be normal, however, because only 20 to 30 per cent of the maximum diffusing capacity is used at rest. Similarly, when 25 per cent of the alveoli are ventilated but not perfused, as in FIGURE 6, maximum diffusing capacity is reduced by 25 per cent. However, when both types of maldistribution occur, one cannot simply add the two defects because they may coexist, as in the middle alveolar unit of FIGURE 10 In other words, one could not assume that because 40 per cent of the alveoli are not ventilated, and 40 per cent are not perfused, that 80 per cent of the alveolar units are not functioning Then only 20 per cent of the normal maximum diffusing capacity could be expected, assuming the alveolar capillary membrane is completely normal. The vital capacity may provide a more conservative estimate of the ventilatory loss, assuming no paralysis of respiratory muscles or other restricting conditions

In FIGURE 10, it can be seen that only 60 per cent of the alveolar units are being ventilated, and that 33 per cent of the ventilated alveoli are not perfused From these figures, one could estimate, at least, that there is a potential blood-gas interphase in no more than two-thirds of 60 per cent, or 40 per cent, of the alveolar units. This type of calculation may be useful in correcting the maximum diffusing capacity to be expected in such a case, thus.

$$[\text{expected max } D_{LO_2}] \times (\%\text{ normal V.C}) \times (100 - \%\text{ alveoli not perfused}) = [\text{"corrected" max } D_{LO_2}] \quad (13)$$

e g , if expected max D_{LO_2} = 80 cc /min /mm Hg for age and body size

then "corrected" D_{LO_2} = 80 × 60% V.C × (100 − 33% not perfused)

= 80 × 40% = 32 cc /min /mm Hg

In this way, measurements of diffusing capacity could be corrected for maldistribution as well as body size and age. Any impairment persisting after these "corrections" could then be

pulmonary vascular disease may be the primary defect.

Poliomyelitis

A large alveolar dead space has also been observed in acute anterior poliomyelitis with respiratory paralysis.[44] In fatal cases, postmortem examination of the lungs has revealed patchy areas of atelectasis and compensatory emphysema, viral pneumonia and occasionally pulmonary edema. However, pulmonary emboli are quite rarely, if ever, seen. Therefore, one must conclude that in this situation the increase in the VA/Q ratios in the patent areas must be so great that, combined with continued perfusion of atelectatic areas, large end-tidal alveolar-arterial CO_2 differences (A-a P_{CO_2}) develop. Usually, these are associated with (A-a P_{O_2}) differences of 40 mm. Hg or more, but they occasionally occur without an increase in the A-a P_{O_2} difference. Effective artificial respiration usually reduces both discrepancies, indicating that more uniform distribution of both gas and blood has resulted.

In acute poliomyelitis the rate of nitrogen washout is not slow, as in emphysema, but accelerated beyond the normal rate.[45] This is probably due to a reduction in functional residual volume in the diseased lungs and provides more support for the interpretation that hyperventilation of the patent areas of the lungs, not underperfusion of normally ventilated areas, causes the high $\dot{V}_A/Q$ ratios observed. Reduced residual volume resulting from acute respiratory muscle paralysis probably also contributes to this fast washout, though no measurements of residual volume in acute poliomyelitis have been reported.

Bronchiectasis

Accelerated or normal rate of nitrogen washout is usually observed in bronchiectasis[4] (Fig. 8). However, in this disease a forced expiration will produce a striking peak of N_2 at any time during the N_2 washout, or at the end of seven minutes of O_2 breathing. In fact, this is characteristic of the disease, probably because so many airways that are blocked by purulent secretions during quiet ventilation can be opened during forced expiration, yielding high concentrations of nitrogen from the previously noncommunicating alveoli. Moderate A-a P_{CO_2} differences of 10 mm. Hg are also frequently observed during quiet breathing in bronchiectasis. The factors causing this phenomenon are probably similar to those operating in poliomyelitis. Pulmonary embolism here is also rare and, therefore, is unlikely to be the reason for the A-a P_{CO_2} differences observed.

Chest Surgery

During open-chest surgery, alveolar-arterial P_{CO_2} differences of considerable magnitude have also been observed.[33] Some of this may, again, be due to overventilation of normally perfused, patent areas as a compensatory phenomenon resulting from collapse of other areas of the lungs. Collapse of large areas is most extensive when the patient has been breathing oxygen for five minutes or so before the chest is opened; the result is that any area which is partially occluded for a short time will have all of the gas in it absorbed by the venous blood perfusing it. If the gas in the alveoli is largely insoluble and inert, such as 79 per cent N_2, the alveoli remain inflated for longer periods of time than if it is readily absorbed. Therefore, if the oxygen concentration is held between 21 to 40 per cent, collapse from absorption of gas beyond obstructions will not be serious. A second precaution taken to minimize the possibility of such collapse is the use of increased resistance to air flow during expiration. A controlled expiratory "back pressure" of 3 cm. H_2O is sufficient to preserve the functional residual volume of the lungs as it existed before the chest was opened.

Pulmonary Capillary Stasis

Another factor which may seriously reduce the efficiency of gas exchange is stasis of blood in the pulmonary capillaries. The physiologic result of insufficient perfusion is an increased A-a P_{CO_2} difference, as described above. This could develop with an intact chest, as in severe polycythemia or sickle-cell anemia, but also has been observed in association with hypothermia, or acidosis during open-chest surgery. Such maldistribution of blood is explained by the fact that all of the above-mentioned conditions can

respiratory gas tensions is that of Riley, using bubble equilibration.[12, 38]

Another approach which is completely bloodless is that of Perkins.[29] Using this method, one samples and analyzes end-tidal alveolar gas continuously and records the readings of an ear oximeter for arterial O_2 saturation simultaneously while the subject breathes different concentrations of oxygen (in exercise, or both). The chief theoretical limitation of this approach is the accuracy of the ear oximeter, however, for practical purposes, it has great value. Again, the equipment required is quite expensive. This method permits differentiation of venous admixture from diffusion impediment as causes of arterial unsaturation, but does not permit calculation of alveolar dead space or the per cent of alveoli which are ventilated but not perfused.

CLINICAL APPLICATIONS

Few parenchymal diseases of the lungs do not alter the intricate pattern of uniform distribution of blood and gas. Some derange it more than others, as will be seen in the following discussion.

Extrinsic Diseases

Disease of the skin, such as scleroderma, or skeletal deformities, such as scoliosis, have surprisingly little influence on the distribution of ventilation. Although such diseases may restrict expansion of the rib cage more in some areas than in others, the distribution of inspired gas has been strikingly uniform in our experience.[41] This would seem to imply that so long as intrathoracic pressure is more or less uniformly distributed, gas will be evenly distributed, even in a badly distorted kyphoscoliotic chest. The distribution of blood is less consistently uniform under these circumstances.

Bronchostenosis

A striking example of maldistribution of inspired gas results from unilateral bronchostenosis. As the patient's frequency of respiration is increased, one can see quite easily how inflation of the partially obstructed lung lags behind the inflation of the good lung; a phase lag of 90 degrees or more may develop in severe cases.[1]

Among the specific tests for this type of difficulty are those sensitive to high resistance to air flow, i.e., 1 second forced expiratory capacity ($FEC_{1.0}$), maximum expiratory flow rate (MEFR), and maximum breathing capacity (MBC). In unilateral bronchostenosis, maximum inspiratory flow rate will also be reduced proportionately, whereas in asthma the reduction in expiratory flow rate is somewhat greater than the reduction of inspiratory flow rate; in obstructive emphysema forced expiratory flow may be stopped almost completely by airway collapse. (The mechanics of respiration are discussed fully in Chapter 37.) The important point to note here is that maldistribution of inspired gas is usually associated with increased resistance to air flow. Conversely, when indices of airway resistance are normal, maldistribution of inspired gas is extremely unlikely. Therefore, tests of airway resistance are useful for screening out patients who are unlikely to have maldistribution.

Emphysema

Emphysema is probably the prime example of a disease in which there is maldistribution of inspired gas. Secondly, there is usually high resistance to expiratory air flow. Increased residual volume is a third finding usually associated with high resistance and maldistribution, and may be largely the result of the distortions of normal mechanics. Since so many other pulmonary diseases can increase resistance to air flow and/or increase residual volume, the most specific physiologic abnormality in obstructive pulmonary emphysema is the maldistribution of inspired gas.[30]

Maldistribution of inspired gas in obstructive emphysema is also usually associated with increased dead space. In the past, very little emphasis has been placed on the nature of this dead space so that many assume that it is simply increased anatomic dead space. However, measurements of end-tidal alveolar CO_2 sampled simultaneously with the arterial CO_2 indicate to us that most of the increased dead space in obstructive emphysema is alveolar.[43] This has interesting implications concerning the pathogenesis of this type of emphysema, suggesting that impaired perfusion resulting from

pulmonary vascular disease may be the primary defect

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cause "sludging," if not frank thrombosis, of blood in the pulmonary capillaries.[9]

Prevention and Treatment of Maldistribution

Maldistribution of blood in relation to gas in the lungs can be minimized by

1 Administering no more than 40 per cent oxygen to a patient with partially obstructed airways or to a patient whose chest is about to be opened for surgery

2 Maintaining normal functional residual volume during open chest surgery by maintaining a minimum pressure of 3 cm H_2O in the airway during expiration

3. Maintaining the hematocrit below 60 per cent in polycythemia

4. Reducing the hematocrit by plasmaphoresis, approximately 1 per cent per degree centigrade below normal body temperature during hypothermia.

5. Preventing hypoxic episodes in any patient, but especially those subject to the sickling phenomenon

6 Using anticoagulants in order to maintain normal or slightly prolonged bleeding and clotting times, if practical, whenever cardiac output is known to be fixed at a low level

7. Maintaining adequate pulmonary blood flow during cardiac bypass or any procedure in which the rate of circulation can be controlled ("adequate" flow here is defined as that which will maintain a mean systemic arterial pressure of no less than 80 mm. Hg and mixed venous oxygen saturation of no less than 50 per cent).

8. Preventing significant acidosis from persisting any longer than necessary, such as may develop insidiously during anesthesia, inadequate cardiac output, or inadequate ventilation, or any of the other more obvious types such as renal or diabetic acidosis.

If these precautions cannot be observed for prolonged periods of time, gas exchange will be inefficient. Under these circumstances sufficient oxygenation of arterial blood can be maintained by use of 40 per cent oxygen, and sufficient carbon dioxide removal can be affected by mechanical hyperventilation, within certain limits. However, one must use arterial blood gas tensions as the criterion of success of these compensatory measures, because alveolar gas analyses may be very misleading and falsely reassuring (FIG. 10).

Miscellaneous Pulmonary Vascular Shunts

Other disturbances of the pulmonary circulation in various disease states are discussed elsewhere in this book. However, the relationship of some of these diseases to our concept of distribution will be covered here

The impressive increase in collateral blood flow in the bronchial circulation (FIG. 11) in certain pulmonary diseases, especially bronchiectasis, has been beautifully delineated anatomically and physiologically by Liebow and co-workers over the years[23] More recently, Fishman has shown that such collateral blood flow, from left to right, may occasionally be impressive, amounting to as much as 20 per cent of cardiac output in some cases[14]

The various paths by which venous blood may gain entrance into the arterial side of the circulation have been studied more thoroughly than has any other aspect of the pulmonary circulation However, a fascinating recent contribution in this field began as a study completely unrelated to the pulmonary circulation[6] Claypool and others have shown that in patients with Laennec's cirrhosis significant arterial hypoxemia can develop from venous blood flowing from the portal venous bed to the pulmonary venous bed via the anastomotic perigastric and periesophageal vessels. This work means that, in searching for an explanation for cyanosis, one should look beyond the lungs to the liver and perhaps other organs if the pulmonary circulation is apparently normal

Maldistribution in Time

Finally, it should be noted that there can be maldistribution of blood in relation to gas in the lungs *in time* as well as *in space* That which has been discussed so far has been concerned with anatomic, spatial relationships However, in periodic respiration, alveolar O_2 and CO_2 tensions can undergo tremendous excursions, resulting in alternating hypoxemia and hyperoxemia, combined with alternating hypercapnea and hypocapnea, respectively. As in spatial maldistribution, the skewed sigmoid shape of the O_2-Hb dissociation curve prevents the high

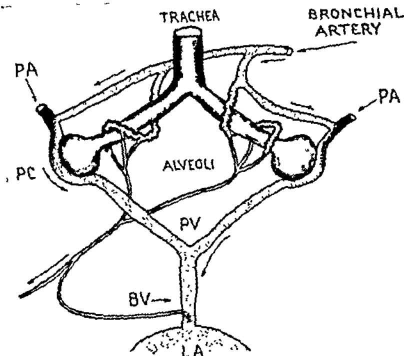


FIG 11.—Left-to-right shunting via the bronchial circulation is depicted as resulting from disease causing increased resistance through the bronchial capillaries, although this is not known to be the case Some bronchial blood gets through to the left atrium (LA) by way of the bronchial veins (BV) Mixed venous blood in the pulmonary arterioles may be partially oxygenated before it reaches the alveoli by the admixture of arterial blood shunted into the pulmonary artery from the bronchial artery

oxygen tension levels from compensating for the low ones, whereas the relatively straight CO_2 dissociation curve permits low CO_2 levels to compensate for high CO_2 The result is hypoxemia in the presence of normal CO_2 tension.

Theoretically, it would be possible for periodic blood flow through the pulmonary capillaries to result in such a wide gamut of $\dot{V}/Q$ ratios in time that significant (A-a P_{CO_2}) differences might develop However, no organism could survive such grossly intermittent flow long enough to make this a significant consideration.

Summary

The distribution of gas and blood in the lungs has been discussed from a theoretical point of view, with references to clinical data, including calculations pertinent to each form of disturbance, under four headings: (1) venous admixture, (2) dead space, (3) maldistribution of inspired gas and (4) maldistribution of blood flow

Methods for the measurement of each type of disturbance are presented briefly. A short but complicated protocol for use in laboratories specializing in pulmonary function testing is described. Finally, clinical situations in which disturbances of distribution may arise are discussed and preventive measures suggested

Acknowledgments

The author wishes to express his gratitude to friends and associates who have been willing to take the time to review and criticize this chapter, though they should not be held responsible for what is finally published These editors behind the scene include Doctors Ward Fowler, C J. Martin, Richard Riley, Max Samter, John Severinghaus and Janet Wolter.

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cause "sludging," if not frank thrombosis, of blood in the pulmonary capillaries.[9]

Prevention and Treatment of Maldistribution

Maldistribution of blood in relation to gas in the lungs can be minimized by

1. Administering no more than 40 per cent oxygen to a patient with partially obstructed airways or to a patient whose chest is about to be opened for surgery.

2. Maintaining normal functional residual volume during open chest surgery by maintaining a minimum pressure of 3 cm H_2O in the airway during expiration.

3. Maintaining the hematocrit below 60 per cent in polycythemia

4. Reducing the hematocrit by plasmaphoresis, approximately 1 per cent per degree centigrade below normal body temperature during hypothermia

5. Preventing hypoxic episodes in any patient, but especially those subject to the sickling phenomenon

6. Using anticoagulants in order to maintain normal or slightly prolonged bleeding and clotting times, if practical, whenever cardiac output is known to be fixed at a low level.

7. Maintaining adequate pulmonary blood flow during cardiac bypass or any procedure in which the rate of circulation can be controlled ("adequate" flow here is defined as that which will maintain a mean systemic arterial pressure of no less than 80 mm Hg and mixed venous oxygen saturation of no less than 50 per cent)

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Evaluation of Alveolar Capillary Diffusion

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THE lung is a relatively compact organ which provides an enormous surface (approximately 50 M.^{2}) for the exchange of gases between the environment and the blood In the latter part of the last century, numerous physiologists attempted to measure the diffusing capacity of the lung in order to prove the existence of gas secretion in the lung. It is now generally accepted that the transfer of gases across the alveolar capillary membrane occurs by simple diffusion.

It was not until shortly after the first World War, however, that investigators (particularly those in Germany) postulated that thickening or destruction of the pulmonary membrane caused desaturation of the arterial blood in certain diseases by interfering with the diffusion of respiratory gases between the alveolar air and the capillary blood. Subsequently, Baldwin provided evidence that where abnormalities in pulmonary mechanics and distribution of inspired gas could be excluded, serious disturbance of diffusion could be demonstrated in some forms of diffuse pulmonary fibrosis Austrian and his colleagues[1] were the first to measure diffusing capacity in this condition and to coin the name alveolar capillary block, thus introducing a physiologic concept to a wide variety of pathologic conditions always associated histologically with involvement of the alveolar capillary septum and physiologically with reduction in the diffusing capacity of the lung This syndrome is discussed in detail in Chapter 51.

General Principles

The molecules of any gas are in constant random motion. Diffusion is the statistical movement of molecules from a region of high to one of lower concentration. In the case of oxygen, molecules move from the higher concentration in alveolar gas to the lower concen- [illegible] in pulmonary capillary blood. According to the ordinary physical laws of diffusion, the rate of passage of a gas across the membrane separating alveolar gas from capillary blood is directly proportional to: (1) the mean difference in partial pressure of the gas on either side of the membrane, (2) the surface area of the membrane, (3) the permeability of the membrane for the gas under consideration This rate is inversely proportional to the thickness of the membrane. The fundamental law of diffusion states that the quantity (Q) of gas transferred per unit of time (t) is proportional to the difference of partial pressure between alveolar gas (P_A) and capillary blood (P_c):

$$\frac{dQ}{dt} \propto P_A - P_c \qquad (1)$$

$$\frac{dQ}{dt} = D(P_A - P_c) \qquad (2)$$

where D is a specific diffusion constant, the diffusing capacity of the lung. For any specific gas this constant becomes a quantitative evaluation of the efficiency of the membrane for diffusion. Equation 2 can be rearranged to obtain pulmonary diffusing capacity

$$D = \frac{\text{Quantity of gas transferred per unit of time}}{\text{Mean differences in partial pressure of gas on either side of membrane}} \qquad (3)$$

The diffusing capacity of the lung (D_L) therefore is defined as the quantity of gas transferred every minute for each millimeter of mercury difference in partial pressure of gas across the membrane The units are ml. of gas at, STPD, per minute per mm Hg gradient in pressure.*

* Roughton and Forster have shown that measurements of pulmonary diffusing capacity usually include [illegible] membrane [illegible]

true diffusing capacity of the pulmonary membrane, D_M, and the measurement which includes diffusion within the blood, D_L. The gas under consideration will be indicated by the subscripts, O_2, or CO

Physical Properties of the Gas Used

The gas used for the measurement of D must be considerably more soluble in capillary blood than in the alveolar capillary membrane. Oxygen and carbon monoxide are the only satisfactory gases available. Also, since D is directly proportional to the solubility of the gas and inversely proportional to the square root of the molecular weight (or density), by combining these laws it can be shown that the diffusing capacity of the membrane for O_2 is 1.23 times that for CO. Hence, if D is known for one gas, it can theoretically be calculated for the other.

Methods

Several methods have been introduced for the measurement of pulmonary diffusing capacity. Each has theoretical and practical advantages and disadvantages. In a short review it is obviously impossible to describe in detail the minutiae of every technic that has been employed or to discuss the entire body of physiologic information that has accrued from their application. The reader is urged to refer to the original articles and to several excellent reviews of the subject that have appeared in recent years. Selected references appear at the end of this chapter.

Oxygen Methods for Measuring Diffusing Capacity

Steady-State D_{LO_2}

$$D_{LO_2} = \frac{\text{ml } O_2 \text{ transferred from alveolar gas to blood per min}}{\text{mean alveolar } O_2 \text{ pressure} - \text{mean capillary } O_2 \text{ pressure}}$$

Therefore, the diffusing capacity of the lung for oxygen could be determined if the oxygen consumption and the oxygen pressure difference between the alveolar air and pulmonary capillary blood were known. The oxygen consumption is measured easily by well established technics. Uneven distribution of inspired gas in pulmonary disease introduces uncertainty concerning the reliability of any expired alveolar sample. However, the mean alveolar oxygen tension can be calculated with reasonable accuracy by use of the alveolar air equation of Rahn. The inaccessibility of pulmonary capillaries presents a real challenge. Direct measurements of pulmonary capillary oxygen tensions are impossible. However, if one knows (1) the alveolar oxygen tension, (2) mixed venous oxygen tension, (3) end-capillary oxygen tension, as well as (4) the physiologic dissociation curve of hemoglobin, it is possible to compute the mean capillary oxygen tension by Bohr's integration procedure.[6] There is no way of obtaining an end-capillary sample for analysis, but arterial blood can be obtained and its oxygen tension measured with reasonable accuracy. Unfortunately, even in normal individuals, arterial blood has a lower oxygen tension than that at the end of the capillary owing to the existence of a physiologic shunt (venous admixture). Thus, the oxygen tension difference between alveolar gas and arterial blood (A-a gradient) includes two components. (1) a "membrane component" due to incomplete equilibrium between alveolar gas and end-capillary blood, and (2) a "venous admixture" component due to contamination of arterial blood by blood from areas with decreased ventilation/blood flow ratios. Lilienthal and Riley[18] have developed a brilliant method for the indirect calculation of end-capillary oxygen tension, which consists of measuring the alveolar-arterial oxygen pressure differences at two levels of oxygenation. By giving the patient 12 to 14 per cent O_2 to breathe, the "venous admixture" component is eliminated almost entirely, the "membrane component" is increased so that it becomes a measurable value, and arterial oxygen tension practically equals end-capillary oxygen tensions. While breathing ambient air, the alveolar-arterial gradient is largely (but not entirely) the result of venous admixture. By trial and error, under rigidly controlled conditions, it is possible to assign values to the "membrane component" and "venous admixture component" which add up to the observed

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convenient graphs prepared by Riley.

The advantages of this method are that it uses the physiologically important gas, oxygen, and that the analytical equipment is relatively inexpensive and suitable for use in a routine chemistry laboratory. On the other hand, the

stringent steady-state conditions required, the technical difficulties encountered in the direct determination of arterial blood gas tensions, the necessity for arterial sampling and the contraindication to breathing low oxygen concentrations in certain conditions have limited the clinical applicability of this technic. Moreover it is necessary to assume that the diffusing capacity, cardiac output and venous admixture are the same at two different levels of oxygenation. The method is fairly accurate when the alveolar end-capillary gradient is large, as in patients with a low diffusing capacity, or in exercise The error is great in normal resting subjects on account of the small alveolar end-capillary gradient which cannot be measured by present technics. In spite of its limitations, some of the most important and stimulating physiologic and clinical research in the past two decades has been done with the D_{LO_2} method

Semi-Quantitative Methods

Provided other causes can be excluded, an increase in the alveolar-arterial oxygen tension difference is an indication of the presence of a defect in diffusion. However, from the practical point of view, it is rare to find a "pure" diffusion defect, and when the apparatus and technical skill required to measure the A-a gradient are available, it only requires a repetition of the procedure while the patient breathes a low oxygen mixture in order to obtain a definitive measure of diffusing capacity. Perkins et al.,[20] however, have developed a useful semi-quantitative method for analyzing the factors that lead to an increase in the A-a gradient The method consists of continuously measuring arterial blood saturation by means of an ear oximeter, and end tidal samples of alveolar gas with an oxygen analyzer over a wide range of safe inspired oxygen concentrations It is particularly useful for measuring rapid changes, such as occur during cardiopulmonary surgery, or acute experiments. However, the expense of the equipment required, the technical difficulties encountered, and the uncertain accuracy of the method limit its clinical utility as a routine measure of pulmonary diffusing capacity.

Qualitative Methods

Methods for measuring arterial oxygen saturation are available in most large hospitals Arterial oxygen saturation may be reduced for many reasons, and a defect in diffusion is only one of these. Moreover, frequently pulmonary diffusing capacity must be less than one-third of normal before arterial oxygen saturation is significantly reduced However, during exercise the arterial saturation will fall below normal because, after maximum dilatation of pulmonary capillaries has occurred, the red blood cells will spend less time than is required to achieve equilibrium with alveolar gas if any further increase in blood flow occurs If arterial oxygen saturation is near normal at rest but falls precipitously with exercise, a defect in diffusion is probably present provided a venous to arterial shunt can be excluded This can be done by repeating the measurement of arterial blood gases while the patient breathes 100 per cent O_2 If arterial saturation rises to 100 per cent and the dissolved oxygen in the plasma rises to 2 ml per 100 ml, a venous to arterial shunt can be excluded

CARBON MONOXIDE METHODS

$$D_{LCO} = \frac{\textit{ml CO transferred from alveolar gas to blood/min}}{\textit{mean alveolar CO pressure—mean capillary CO pressure}}$$

It occurred to Bohr[6] that carbon monoxide might be a uniquely suitable gas for the measurement of diffusing capacity because of its tremendous affinity for hemoglobin (about 220 times that of oxygen) He assumed that the rate of combination was practically instantaneous so that as CO diffused into the plasma it was removed so rapidly that, if relatively low concentrations of CO were used, the capillary CO tension would be so small that it could be safely neglected. The gradient of CO pressure across the membrane at any instant should then be equal to the partial pressure of CO in alveolar gas. This obviates the need for complicated procedures necessary to compute mean capillary tensions and immensely simplifies the calculations of D_{LCO} compared with D_{LO_2}. In order to calculate D_{LCO}, one need only know

the rate of CO uptake in the lungs and the mean alveolar CO tension, both of which can be measured readily.

Steady-State Methods

$$D_{L_{CO}} = \frac{\text{ml CO transferred from alveolar gas to blood/min.}}{\text{mean alveolar CO pressure}}$$

In this technic the patient breathes air containing approximately 0.1 per cent CO. After several breaths (about 12) the alveolar CO tension reaches a plateau and the measurements are made. The amount of CO transferred from alveolar gas to capillary blood is simply found by subtracting the measured quantity of expired CO from that inspired during a known period of time under steady state conditions. The critical measurement, alveolar CO tension, can be measured in an alveolar sample or calculated from independent estimates of either anatomic or physiologic dead space, together with measured inspired and expired CO tensions.

Alveolar sample $D_{L_{CO}}$. Although collecting an expired alveolar sample is the most direct method, the Kroghs[13] calculated that the alveolar CO tensions so obtained could vary by as much as 25 per cent. On the other hand, Bates has found that, if the rate and depth of breathing are constant, a continuous end-tidal sampling technic gives satisfactory results.

Anatomic dead space $D_{L_{CO}}$ (Bohr). Alveolar CO tension can be calculated from the Bohr relation,

$$\text{Alveolar CO tension} = \frac{\text{expired tidal volume} \times \text{expired } P_{CO} - \text{dead space volume} \times \text{inspired } P_{CO}}{\text{expired tidal volume} - \text{dead space volume}}$$

However, this method is unreliable when tidal volume is small, since even slight differences in the estimate of anatomic dead space create large differences in the calculated alveolar CO tension. During exercise or when tidal volume is large, the method is more precise.

Physiologic dead space $D_{L_{CO}}$ (Filley). Alveolar CO tension can also be calculated from the physiologic dead space using the method described by Filley,[9] in which

$$\text{Alveolar CO tension} = \text{inspired } P_{CO} - \frac{\text{arterial } P_{CO_2}}{\text{expired } P_{CO_2}} \times \left(\text{inspired } P_{CO} - \text{expired } P_{CO}\right)$$

The alveolar CO tension obtained by this technic is least reliable when tidal volume is small and diffusing capacity large, or when ventilation/blood flow relationships are not uniform throughout the lung. According to Filley et al., the error in resting values is not likely to be more than 25 per cent. As with the previous method, the error is less during exercise.

The steady state methods for measuring $D_{L_{CO}}$ are performed under normal physiologic conditions, require very little cooperation from the patient, and can be applied to even seriously ill patients. As pointed out above, the greatest difficulty lies in selecting a representative alveolar CO tension. In spite of theoretical objections, modifications of the physiologic dead space method have found wide acceptance. An infrared analyzer is more reliable than the original chemical methods. From a practical point of view, the most serious drawbacks are the necessity for arterial sampling and accurate blood gas analysis. Bates' end tidal sampling technic circumvents this problem but has not yet found such general acceptance as the Filley technic.

Breath-Holding Methods

Krogh $D_{L_{CO}}$. In 1909, the Kroghs[13] described a method for measuring $D_{L_{CO}}$ during a period of breath-holding at a constant alveolar volume. The subject made a rapid inspiration from residual volume of a gas mixture containing 1 per cent CO and rapidly expired an alveolar sample (initial alveolar P_{CO}), followed in about six seconds of breath-holding by a second alveolar sample (final alveolar P_{CO}). They also devised an equation which described the disappearance of CO from alveolar gas during breath holding and from which they were able to calculate $D_{L_{CO}}$.[14]

$$\text{Final alveolar } P_{CO} = \text{initial alveolar } P_{CO} \times e^{(-D_{L_{CO}}(B-47)t/V_A)}$$

This equation is not as formidable as it may appear, and simply states in mathematical terms that for any alveolar volume (V_A) at any barometric pressure (B) alveolar P_{CO} decreases exponentially with time (t), the exponential

constant* being the diffusing capacity of the lung ($D_{L_{CO}}$).

Modified Krogh $D_{L_{CO}}$ (Forster) Where the distribution of inspired gas is uneven, the differing initial concentrations of CO in the two expired alveolar samples used in the Krogh technic are likely to result in an overestimate of $D_{L_{CO}}$. Fowler suggested modifying the technic by using an inspired gas mixture containing, in addition to CO, the inert relatively insoluble gas helium and collecting only one expired alveolar sample. From the fractional dilution of inspired helium by the residual gas in the lung, it is possible to calculate the initial alveolar CO concentration or tension

$$\text{Initial alveolar } P_{CO} = \text{inspired } P_{CO} \times \frac{\%\ \text{expired He}}{\%\ \text{inspired He}}$$

The resting, seated subject makes a maximal inspiration from residual volume of a gas mixture containing approximately 0 3 per cent CO, 10 per cent He, 21 per cent O_2 and the remainder N_2, and an alveolar sample obtained from the expirate after a 10 second period of breath-holding. The first liter of expired gas is discarded and the remainder considered uncontaminated by dead space gas [19]

$$D_{L_{CO}} = \frac{\text{Alveolar volume} \times 60}{\text{Time in seconds} \times (\text{barometric pressure} - 47)} \times \text{Natural logarithm} \frac{\text{initial CO concentration}}{\text{expired CO concentration}}$$

According to Forster et al, the coefficient of variation of the measurements in any individual is about 6 per cent The test is rapid, reproducible and can be repeated several times within a few minutes Forster found that the disappearance of CO from the lung was not truly exponential, i e., $D_{L_{CO}}$ apparently decreased with time. The most likely explanation is the differing $D_{L_{CO}}$ throughout the lung Hence, a period of breath-holding of 10 seconds was arbitrarily chosen because it gave comparable values and because all but the most seriously ill patients could hold their breath for this period of time. The estimation of $D_{L_{CO}}$ obviously depends on the part of the lung sampled, if $D_{L_{CO}}$ varies throughout the lung as would be expected in patients with lung disease. Hence, the breath-holding technics have been criticized on theoretical grounds by many competent physiologists. However, the writer, while recognizing the theoretical objections to this technic, has not found that they significantly limit its practical utility. During the past three years his laboratory has made more than 3000 measurements of diffusing capacity in patients and normal subjects at breath-holding times between 5 and 20 seconds In no instance did the results lead to a faulty clinical impression On the contrary, this method frequently demonstrated abnormalities not detected by other technics Furthermore, the reproducibility of results, even when the time of breath-holding varied by a factor of 2 or 3, was very similar in patients and in normal subjects The writer can only conclude that where $D_{L_{CO}}$ varies throughout the lung (as is likely, for example, in patients with pulmonary emphysema), areas with a high or low diffusing capacity contribute proportionately to any expired alveolar sample In other words, the ratio of final alveolar P_{CO}/initial alveolar P_{CO} obtained in an expired alveolar sample is reasonably representative of the lung as a whole in patients as well as normal subjects Variations in intra-alveolar pressure and pulmonary blood flow during the test or differing levels of lung inflation might be expected to affect the reproducibility of the calculated $D_{L_{CO}}$ In a series of experiments in young normal subjects at lung volumes between functional residual capacity and total lung capacity and intrathoracic pressures between 30 mm Hg below and 60 mm. Hg above atmospheric pressure, the average range of $D_{L_{CO}}$ was 15 per cent. Although these studies have not been applied to patients, it is unlikely that the moderate deviations from maximum lung inflation and the variations in intrathoracic pressure found during ordinary clinical testing will significantly affect the results.

Rebreathing Methods

In 1954, Kruhøffer[15] described an original and very useful method for measuring $D_{L_{CO}}$

* M Krogh called the entire exponential constant K, which is equal to $D_{L_{CO}}$ (B-47)/V_A, the permeability of the lung.

during a 30 second period of rebreathing from a 6 liter bag containing a very low concentration of radioactive-labeled $C^{14}O$. The rate of disappearance of CO was determined by taking gas samples from the system at intervals between 12 and 30 seconds of rebreathing. By adding 20 per cent hydrogen to the original gas mixture and measuring its change in concentration after equilibration with lung gas, he was also able to determine the lung volume. Hence, D_{LCO} could be calculated from an equation identical to that used in the breath-holding technics. Where the respirations were rapid and deep enough, P_{CO} decreased exponentially, and theoretically the calculated D_{LCO} could be shown to be unaffected by uneven distribution of inspired gas, alveolar volume, or alveolar diffusing capacity.

This technic merits more widespread use since it is relatively easy to perform, does not entail arterial blood gas analysis, and circumvents several problems inherent in the breath-holding technics. On the other hand, the rapid breathing required introduces several theoretical and practical objections, particularly in patients with lung disease. There is no particular advantage in the use of labeled CO and, in most instances, helium would be preferred to hydrogen for the measurement of alveolar volume.

Semi-Quantitative Methods

Several indices of diffusion have been introduced which depend on the fractional CO uptake.

$$\textit{Fractional CO uptake} = \frac{\textit{CO absorbed}}{\textit{CO inspired}} \times 100$$

Unfortunately, fractional CO uptake, which is normally about 50 per cent, varies over a wide range depending on the minute ventilation and tidal volume. The test is relatively simple, but provides only a rough index of diffusion. There appears to be little merit in calculating some crude index of diffusion when much more useful and precise measures of diffusing capacity can be obtained with very little extra effort.

Pulmonary Diffusing Capacity in Healthy Subjects

The normal resting values for healthy subjects depend on the technic employed. The average values reported by different investigators are listed in Table 1. It is obvious that each method measures something different, and probably none precisely measures the diffusing capacity of the pulmonary membrane. Forster and Roughton[25] have shown that the diffusing capacity of the pulmonary membrane is probably twice as large as conventional technics suggest. Nonetheless, all technics have been shown to provide useful comparative estimates of the efficiency of alveolar-capillary diffusion. The steady-state methods tend to give lower resting values than the breath-holding or rebreathing methods and tend to increase proportionately more with exercise. Several investigators using steady-state methods have reported fairly good agreement between D_{LO_2} and $D_{LCO} \times 1.23$, but it is doubtful if current methods are precise enough to be certain that this relationship is more than fortuitous. As would be expected, pulmonary diffusing capacity varies with body size. From data reported in the literature, Forster[11] concluded that D_{LO_2}

Table 1.—*Normal Values for D_{LO_2} and D_{LCO} Reported by Various Investigators*

Method	No. of Subjects	Diffusing Capacity ml./min./mm. Hg	
		Average	Range
A. Oxygen Methods			
Bohr (1909)	1	16.0	
Lilienthal (1946)	6	21.0	12–36
B. Carbon Monoxide Methods			
1. Steady State D_{LCO}			
a. alveolar sample D_{LCO}			
Forbes (1945)	2	34.5	30–39
Gilson (1955)	3	32.4	27–55
Bates (1955)	19	17.6	10.5–28.7
b. Physiologic Dead Space D_{LCO}			
Hatch (1952)	6	19.0	
Filley (1954)	7	16.9	10.5–28.0
Marks (1957)	13	19.5	15.6–26.8
2. Breath-Holding D_{LCO}			
Krogh (1914)	22	26.5	16.8–35.0
Bates (1956)	6	16.8	12.0–22.0
Ogilvie (1957)	28	24.9	11.0–37.5
Marks (1957)	13	30.2	21.5–34.3
Rankin (1959)	43	29.6	21.4–39.0
3. Rebreathing D_{LCO}			
Kruhoffer (1954)	15	25.3	19.5–31.0

constant* being the diffusing capacity of the lung (D_{LCO})

Modified Krogh D_{LCO} (Forster). Where the distribution of inspired gas is uneven, the differing initial concentrations of CO in the two expired alveolar samples used in the Krogh technic are likely to result in an overestimate of D_{LCO}. Fowler suggested modifying the technic by using an inspired gas mixture containing, in addition to CO, the inert relatively insoluble gas helium and collecting only one expired alveolar sample. From the fractional dilution of inspired helium by the residual gas in the lung, it is possible to calculate the initial alveolar CO concentration or tension

$$\textit{Initial alveolar } P_{CO} = \textit{inspired } P_{CO} \times \frac{\%\ \textit{expired He}}{\%\ \textit{inspired He}}$$

The resting, seated subject makes a maximal inspiration from residual volume of a gas mixture containing approximately 0.3 per cent CO, 10 per cent He, 21 per cent O_2 and the remainder N_2, and an alveolar sample obtained from the expirate after a 10 second period of breath-holding. The first liter of expired gas is discarded and the remainder considered uncontaminated by dead space gas.[19]

$$D_{LCO} = \frac{\textit{Alveolar volume} \times 60}{\textit{Time in seconds} \times (\textit{barometric pressure} - 47)} \times \textit{Natural logarithm} \frac{\textit{initial CO concentration}}{\textit{expired CO concentration}}$$

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In 1954, Kruhøffer[15] described an original and very useful method for measuring D_{LCO}

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TABLE 2.—*D_L and Several Other Pulmonary Function Tests in Patients with Various Disorders Usually Associated with Abnormalities in Alveolar-Capillary Diffusion*

	VC %	RV %	TLC %	MBC %	Mixing Index % N_2	Arterial O_2 Saturation %	Arterial CO_2 Tension mm Hg	Diffusing Capacity ml/min/mm Hg		
								Observed	Predicted	%
Diffuse interstitial pulmonary fibrosis										
1. Hamman-Rich syndrome (moderate severity)	74	75	74	138	1.0	93.6	31	14.8	29.6	50
2. idiopathic pulmonary fibrosis (severe)	58	171	80	30	0.5	69.4	42	4.0	21.1	19
Pulmonary granulomas										
3. sarcoidosis (discrete nodular disease)	126	69	113	142	1.0	95.4	35.4	27.8	32.0	87
4. sarcoidosis (diffuse disease)	71	57	71	66	1.5	89.7	29.8	12.1	28.8	43
Chronic obstructive pulmonary emphysema										
5. emphysema (moderate severity)	58	461	170	22	12.0	89.9	42.5	17.3	26.8	65
6. emphysema (severe)	55	329	143	20	18.4	81.9	53.0	9.4	25.2	37
Heart disease										
7. mitral stenosis with moderate pulmonary hypertension	105	243	142	104	1.0	97.4	33.4	12.4	20.3	61
8. mitral stenosis with marked pulmonary hypertension	113	154	119	78	0.5	97.3	—	19.5	28.1	69
Variations in pulmonary blood flow										
9. atrial septal defect with large pulmonary blood flow	135	86	125	75	0.5	96.7	31.5	45.2	36.7	123
10. multiple pulmonary emboli	83	64	77	85	0.3	96.2	28.3	17.3	27.9	62
Variations in circulating hemoglobin										
11. polycythemia (Hb 24.3 Gm/100 ml)	118	186	139	82	0.8	89.5	24.5	53.2	32.2	165
12. anemia (Hb 5.4 Gm/100 ml)	108	184	135	110	1.0	—	—	13.8	24.1	57

According to Ogilvie et al., the predicted value for D_L = surface area (in square meters) × 18.85 − 6.8. Other normal values are according to the methods of Darling, Baldwin and Cournand (see Chapter 36).

Although the causes were numerous, the syndrome had distinct physiologic features. These patients characteristically had a relatively normal maximum breathing capacity, hyperventilation at rest, reduced static lung volumes and an arterial oxygen saturation that was normal at rest and fell markedly with exercise. Their results were amply verified by later investigators, thus was added a physiologic concept which has contributed considerably to our understanding of these diseases. A few examples (1–4) are given in TABLE 2. For a more complete description of this syndrome, the reader should turn to Chapter 51. Case 1 represents a moderately severe defect in diffusion proved on lung biopsy as due to the Hamman-Rich syndrome. Case 2, suffering from diffuse nonspecific interstitial pulmonary fibrosis, demonstrates a more advanced stage of disease. In this patient there was, in addition to the defect

(or $D_{LCO} \times 1.23$) appeared to increase as a linear function of body surface area, increasing approximately 12 ml./min./mm. Hg/M.² in the case of steady state methods and approximately 18 ml./min./mm. Hg/M.² in the case of breath-holding methods. In view of their lower basal metabolic rate, it is not surprising that women have a slightly lower diffusing capacity than men of the same size. Using a modified breath-holding technic, we found that the diffusing capacity for women was 15.9 ml./min./mm. Hg/M.² and for men 17.8 ml./min./mm. Hg/M.² However, with present technics the differences are, in general, too small to be of practical importance. Likewise, there appears to be no consistent difference in resting values with age. However, older subjects usually cannot increase their diffusing capacity on exercise to the same extent as younger subjects of the same size. This difference has been attributed to a lower cardiac index and decrease in the size of the pulmonary capillary bed in later decades of life. According to Riley,[7] maximal diffusing capacity decreases with age, according to the following regression equation

$$D_{LO_2} = 0.67\ (\text{height in cm.}) - 0.55\ (\text{age in yr.}) - 40.9$$

Pulmonary diffusing capacity is also influenced by a number of physiologic variables. The effects of variations in the level of lung inflation, alveolar ventilation, intrathoracic pressure, and distribution of inspired gas have already been discussed. The volume of the capillary bed appears to vary with change of body position; hence, there is a 14 to 20 per cent[4, 19] increase in supine compared with sitting values.

Of considerable interest in recent years has been the demonstration that variations in respiratory gas concentrations significantly influence D_{LCO}. At an alveolar oxygen tension of 600 mm. Hg, D_{LCO} is approximately one-half that at an alveolar tension of 100 mm. Hg. Roughton and Forster[25] have concluded that the decrease in D_{LCO} as alveolar P_{O_2} rises is the result of a decrease in the rate at which the red cell can take up CO, and that at least one-half of the total resistance to CO diffusion into the blood at a very high alveolar P_{O_2} lies between the surface and the interior of the red cell. The diffusion of CO into the blood can be considered as made up of two parts, that across the pulmonary membrane and that inside the capillary. By means of an ingenious technic, which includes the measurement of D_{LCO} at several different alveolar oxygen tensions and the graphic solution of a simple linear equation,* Roughton and Forster have shown that it is possible to calculate the "true" diffusing capacity of the pulmonary membrane (D_M) and the average volume of the pulmonary capillary bed (V_C). For subjects with a body surface area of approximately 2 M.² and a diffusing capacity of 32.1 ml./min./mm. Hg values for D_M of 63.5 ml./min./mm. Hg and V_C of 97.3 have been reported.[15] Further discussion of this imaginative research is beyond the scope of this chapter, but it can be confidently anticipated that extension and application of these technics will lead to a better understanding of pulmonary gas exchange, both in health as well as disease. Probably of less importance but of some interest is the fact that breathing 7.5 per cent CO_2 for 10 minutes increases D_{LCO} approximately 25 per cent.[21] This increase appears to be partly the result of a direct effect on the vessels as well as an increase in pulmonary blood flow.

Pulmonary Diffusing Capacity in Disease

Since the early part of this century it has been postulated that certain diffuse forms of pulmonary fibrosis produced pulmonary insufficiency by interfering with the diffusion of respiratory gases between alveolar air and pulmonary capillary blood. Austrian and his colleagues[1] were the first to measure pulmonary diffusing capacity in a group of pathologic conditions always associated histologically with involvement of the alveolar capillary membrane. They found markedly decreased values for pulmonary diffusing capacity and coined the name "alveolar capillary block" syndrome.

* According to Roughton and Forster

$$1/D_L = 1/D_M + 1/\theta V_C$$

where D_L is the diffusing capacity of the lung for CO; D_M is the true diffusing capacity of the pulmonary membrane, V_C is the volume of blood within the pulmonary capillaries, and θ is the in vitro rate of combination of CO with intracorpuscular hemoglobin.

increased, normal, or decreased values. The variability of the findings in patients with mitral stenosis is related to the relative effects of this disease on the pulmonary membrane and capillary bed Where the capillary bed is congested and the membrane relatively normal, D_L may be increased. On the other hand, where there is pulmonary hypertension, increased pulmonary vascular resistance, and a reduction in pulmonary blood flow, D_L may be significantly reduced. In other instances, the relative changes in the membrane and capillary bed result in a normal D_L. Pathologic studies have shown that, while the pulmonary capillaries are dilated in the early stages of the disease (increased D_L), subsequently there is an increase in the thickness of the pulmonary membrane (decreased D_L). Cases 7 and 8 have very similar pulmonary diffusing capacities in spite of the fact that the latter had much more severe hemodynamic abnormalities Utilizing the technique of Roughton and Forster,[25] it was shown that, although the pulmonary membrane in Case 8 was much more abnormal than in Case 7, congestion of the capillary bed (capillary volume 3 times normal) tended to obscure the gross abnormality in the membrane. Pulmonary arterial hypertension or obstruction of portions of the vascular bed of the lung by emboli (Case 10) result in reduction of D_L without much alteration in other tests of pulmonary function. Conversely, a marked increase in pulmonary blood flow, such as occurs in a patient with a patent ductus arteriosus or a ventricular or atrial septal defect (Case 8), will result in a significant increase in D_L. In fact, all patients with uncomplicated left-to-right cardiac shunts usually show this increase. A decreased D_L in such patients indicates the presence of pulmonary arterial hypertension. Other circulatory disorders have yet to be studied.

It should also be noted that marked alterations in the quantity of circulating hemoglobin may profoundly affect diffusing capacity for CO and perhaps also for O_2. Rankin et al [22, 23] have shown that anemia (Case 12) may decrease $D_{L_{CO}}$ to as little as one-third of normal, without detectable change in the pulmonary membrane. Conversely, the increased quantities of circulating hemoglobin found in patients with polycythemia rubra vera (Case 11) should increase $D_{L_{CO}}$. However, not all patients show this increase, presumably because of abnormality in the pulmonary membrane or thrombosis in portions of the vascular bed of the lung.

Conclusions

Measurement of the diffusing capacity of the lung is one of the most valuable tests of pulmonary function. All methods provide useful (albeit slightly different) information concerning the efficiency of gas exchange across the alveolar capillary membrane. However, because of their reproducibility and relative simplicity, the methods which utilize carbon monoxide as the test gas have the greatest clinical utility. In general, the measured values obtained are in accord with current concepts of the physiologic abnormalities of the pulmonary membrane and capillary bed.

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in diffusion, pulmonary arterial hypertension, gross abnormality in the distribution of blood flow, and cardiac failure In several instances, investigators have been disturbed because, in spite of striking x-ray changes, diseases usually associated with alveolar capillary block have occasionally failed to reveal a reduction in diffusing capacity by one or other technic However, this should come as no surprise to the clinician Diseases such as sarcoidosis may occasionally produce discrete nodular lesions as distinct from diffuse disease. As a result of the former, intervening areas of the lung are perfectly normal and produce no measurable abnormality in diffusion Cases 3 and 4 illustrate the point. Although the x-ray abnormalities were equally striking, the lesions in Case 3 were more definitely nodular compared with those in Case 4, which were very diffuse Also, we have found significant reduction in pulmonary diffusing capacity due to diffuse involvement of the alveolar capillary membrane (proven by lung biopsy) when chest x-rays have been reported as normal As the result of studying more than 200 patients with diseases usually included in the alveolar capillary block syndrome as well as several hundred patients with other cardiopulmonary disorders, we feel that, in general, there is excellent correlation between damage to the pulmonary membrane and a decrease in diffusing capacity In our hands, this has been one of the most valuable tests of pulmonary function The measured value for pulmonary diffusing capacity cannot, however, be interpreted correctly without correlation with the other available physiologic and clinical information.

Perhaps the greatest controversy between proponents of the several methods of measuring pulmonary diffusing capacity concerns the significance of these measurements in patients with chronic obstructive pulmonary emphysema. In this disease, there is considerable abnormality in all aspects of lung function, and histologic studies have been reported to show destruction of alveolar septa and capillary walls Hence, there should be considerable loss of surface area available for diffusion. In line with this argument, Bates et al.[5] have concluded that $D_{L_{CO}}$ is the most sensitive guide to prognosis. In advanced cases, a reduction in diffusing capacity can be demonstrated by any method of measurement. However, in less severely affected patients the steady state methods tend to show a greater reduction in D_L than the breath-holding or rebreathing methods. The reason for this difference has not been elucidated. It is uncertain how much the abnormalities in pulmonary gas exchange found in this disease are related to the loss of alveolar capillary surface area available for diffusion or to the distributional abnormalities present. In the writer's experience, the outstanding physiologic defects result from uneven distribution of alveolar ventilation and volume in relation to pulmonary blood flow rather than to loss of surface area for diffusion Case 5 (Table 2), a moderately severe case of emphysema, has a moderate decrease in pulmonary diffusing capacity, while Case 6 is an example of advanced pulmonary emphysema with arterial anoxia, CO_2 retention, pulmonary arterial hypertension and impending heart failure. Resting values for the modified breath-holding technic are infrequently below 40 per cent of normal unless the pulmonary vascular bed is seriously compromised A reduction of $D_{L_{CO}}$ out of proportion to the ventilatory and distributional abnormalities, in any case, suggests the presence of an associated interstitial pneumonitis or diffuse pulmonary fibrosis This interpretation has been substantiated by lung biopsy on several occasions With these exceptions, however, measurements of pulmonary diffusing capacity correlated reasonably well with the severity of the clinical picture in chronic obstructive pulmonary emphysema Bronchial asthma unassociated with emphysema does not produce any significant change in D_L.[2]

Measurements of pulmonary diffusing capacity may provide information concerning the vascular bed of the lung They are particularly helpful in cardiovascular disorders which produce alterations in the capillary bed of the lung or which affect pulmonary blood flow. Studies performed on patients with mitral stenosis have produced variable results. In most instances, decrease in diffusing capacity correlates with an increase in pulmonary vascular resistance. However, the writer has found patients with

The Pulmonary Circulation

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For every living animal cell, respiration is that vital process which accomplishes the uptake of oxygen and the removal of carbon dioxide. In unicellular organisms, this gaseous exchange occurs through the cell membrane which is in direct contact with the environment. More complex organisms such as insects require a system of air ducts, called tracheae, with many openings on the body surface and branches which penetrate to contact all tissues. Oxygen and carbon dioxide diffuse through these tubes, so that in a sense, the internal cells and the atmosphere remain in direct contact. In air-breathing vertebrates with their greater body dimensions, a specialized gas transport mechanism has been evolved which is interposed between the internal cells and the atmosphere. This consists of blood, which is characterized by the presence of the respiratory pigment hemoglobin which binds oxygen chemically but reversibly and thus transports this gas in a highly efficient manner. Gaseous exchange between blood and the atmosphere is facilitated by the enormous aerating surface provided by specific organs called lungs The gas-bearing blood is then propelled by the circulatory system, whose ramifications bring the blood into intimate contact with the internal cells of the organism. Thus, in the over-all plan to provide for the respiratory demands of the organism, the primary function of the pulmonary circulation is to oxygenate and remove carbon dioxide from a large volume of blood in a short period of time by means of a vast aerating surface.

Embryology

The anatomic relationships between the pulmonary and the systemic circulations are best understood when approached phylogenetically.[15] In such primitive creatures as amphioxus, the intestinal tube is the respiratory organ. The vascular supply of this tube consists of branches from the aorta, which thus function as the afferent respiratory vessels In the human embryo, the respiratory organ begins similarly as a ventral outpouching of the foregut. This is supplied directly and exclusively by the seventh through the twelfth tributaries of the dorsal aorta. From these vessels, the postbranchial plexus develops. A ventral channel then forms within this plexus, still with *only direct connections* with the aorta. Next, the sixth aortic arch develops a ventral bud which grows caudally and simply anastomoses with this vascular channel, thereby forming the "pulmonary artery" (Fig 1). Thus, the blood vessels of the lung communicate *originally* with the dorsal aorta, and later also with the sixth aortic arch, one-half of which is destined to become the pulmonary artery.[15] Most of the original tributaries from the aorta disappear, and only two or three persist as the adult bronchial arteries. However, when the anastomosis between the sixth arch and the postbranchial plexus fails to develop, resulting in atresia of the pulmonary artery, then the lung vessels retain their original connections with the aorta, and numerous large bronchial arteries are found supplying that lung. On this developmental basis, the intimate relationships between the pulmonary and the bronchial circulations become obvious.

Anatomy

The entire output of the right ventricle is distributed to the pulmonary capillary bed by means of a branching system of large elastic arteries, smaller muscular arteries and arterioles. These are true end arteries with no anastomoses between adjacent arterial branches. By contrast, the pulmonary veins intercom-

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arterioles have walls less than 5 per cent of the lumen diameter, and with little or no discernible smooth muscle, except at their proximal end

Small Arteries

In contrast to the arterioles, the small muscular arteries of the pulmonary circulation, with diameters between 1 0 and 0 1 mm, may have considerable musculature In fetal life, they have a wall thickness which exceeds the diameter of the lumen and are characterized by a thick muscular media Normally, this muscle layer regresses following birth, so that the wall thickness is less than the diameter of the lumen before six months of age However, in certain types of congenital heart disease with associated pulmonary hypertension, the small muscular arteries may retain their thickened media[8] When stimulated to constrict, these muscular vessels can produce a high vascular resistance to blood flow

The basic function of the lung, the oxygenation of blood, is performed at the alveolar capillary level One may therefore think of the alveolus and its surrounding capillaries as a "functional unit" The dimensions of this unit are determined by physical laws The rate of diffusion in the gas phase must impose an upper limit to the distance between an oxygen molecule in the alveolus and a red blood corpuscle in the capillary, which cannot be exceeded if efficient oxygenation is to occur Furthermore, there are other configurational limits The capillary must be large enough to accommodate a red corpuscle, while the terminal airway must be large enough to permit the mass movement of air From these considerations, it follows that the dimensions of the "functional unit" must be fairly constant and independent of the ... [illegible] ...nate a larger ... r number of "functional units

On the basis of this hypothesis, one may speculate on the manner in which the human lung increases in size as the entire body grows to a mass 20 times the birth weight Obviously, the lung of the newborn is not simply a miniature model of the adult lung For the airway system, growth is accomplished by successive branching of the original embryonic lung bed.[31] At birth, there are 17 generations of these branches in the human lung[25] After birth, the smaller airways continue to subdivide at least through middle childhood to produce the final number of about 24 generations.[4, 5, 33] Similar postnatal growth patterns have been described for the mouse and the cow. With this increase in the absolute number of terminal airways and alveoli after birth, there must be a concomitant increase in the number of capillaries, i.e., an increase in "functional units." How far proximal or distal to the capillary bed does the "functional unit" extend? Does it include the arterioles, and perhaps even the small muscular arteries? This is a reasonable possibility, since the smaller muscular arteries accompany the alveolar ducts, while the arterioles accompany the alveolar sacs[4] Such a growth pattern would have far reaching implications with respect to the pulmonary circulation, but until detailed quantitative histologic studies have been carried out, the true nature of lung growth must remain a matter of speculation

Lymphatics

In both normal and diseased lungs, the routes of lymph flow have been carefully studied by Tobin[34] He found that the principal lymph drainage is along the bronchi and pulmonary arteries in a centripetal direction toward the hilar region Secondary routes from the lung periphery and pleura accompany the pulmonary veins to the hilum It is these channels which dilate to serve as collaterals when the primary lymphatics become obstructed, or in pulmonary edema

From the hilar nodes, the lymph drains into the thoracic duct This is unidirectional flow away from the lung, as evidenced by the presence and direction of valves in these lymphatics

Within the pulmonary ligament, there are communications between the pulmonary and mediastinal lymphatics, which can also serve as collateral channels under certain conditions.

Innervation

Both sympathetic and parasympathetic nerves supply the pulmonary blood vessels with afferent and efferent fibers[33] The sympathetic pulmonary filaments are derived from the second to the sixth thoracic ganglia and run

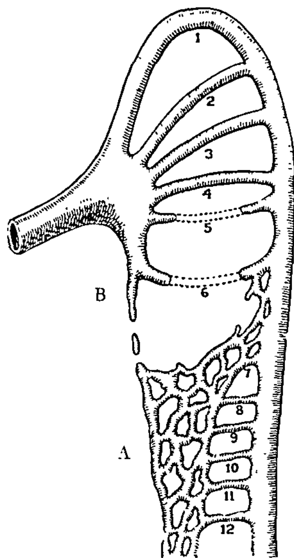


Fig 1—Developmental anatomy of the lung. Tributaries of the dorsal aorta supply the postbranchial plexus (A) which ultimately becomes the pulmonary vascular bed The pulmonary artery originates as a ventral bud (B) from the sixth aortic arch, grows caudally, and simply anastomoses with the postbranchial plexus (after Huntington[14])

municate freely. In addition, pulmonary arteriovenous shunts may also exist. Von Hayek[11] has described "Sperrarterien," cork-screw-like vessels located as if they were intended to function like valves regulating flow through these arteriovenous anastomoses Such an arrangement would enable these vessels to play an important role in intrapulmonary circulatory adjustments. However, until such time as the "Sperrarterien" can be studied in the living lung, their true function and control will remain uncertain.

A second system of blood vessels, the bronchial arteries and veins, contribute to the pulmonary circulation. Usually there are two bronchial arteries to the left lung and one to the right, which originate on either the ventral side of the upper thoracic aorta, or from the upper aortic intercostal arteries. From the right lung, the bronchial veins drain into the azygos vein, while from the left lung, they drain into either the accessory hemiazygos vein or the highest intercostal vein.

Intercommunications exist between the bronchial and the pulmonary vessels[26, 32] There are precapillary anastomoses between the bronchial and pulmonary arteries, which dilate in the presence of inflammatory disease, or following experimental ligation of the pulmonary artery.[22] We have obtained fully oxygenated blood from the proximal pulmonary artery of a lung with advanced tuberculosis. Similarly, Liebow[19] has demonstrated postcapillary anastomoses between the two venous systems, which can enlarge tremendously in emphysema

Histology

Capillaries

One of the most unique features of the pulmonary circulation is its vast network of capillaries suspended freely among the air spaces. The blood in these capillaries is separated from the alveolar air by only two layers of cells, the capillary wall and the alveolar membrane, according to the electron microscopy studies of Low.[20] Thus, there are virtually no confining tissues surrounding the pulmonary capillary bed The total volume of blood in the capillaries can therefore change markedly as the gross dimensions of the lung change with respiration. Riley has postulated the paradoxical relationship that with inflation of the lung, the volume of blood in the capillaries decreases, while the volume of blood in the larger vessels, and hence the total pulmonary blood volume, increases; the converse would occur with deflation[5]

Arterioles

Pulmonary arterioles, defined as being less than 100 micra in diameter, are histologically most unimpressive when compared with systemic arterioles. Whereas the latter have muscular walls with a thickness 30 to 40 per cent of the diameter of the lumen, the pulmonary

extremely valuable tool in the study of the pulmonary circulation. With a catheter in the pulmonary artery, one can take advantage of the blood oxygenating process to calculate pulmonary blood flow. Applying the law of the conservation of matter, the amount of oxygen entering the lungs by way of the airways (oxygen uptake) and the pulmonary arteries (mixed venous oxygen concentration times flow) at any instant must equal the amount of oxygen leaving the lungs by way of the pulmonary veins (arterial oxygen concentration times flow) during that same instant. In actual practice, blood samples are drawn from the pulmonary and brachial arteries during the simultaneous measurement of oxygen uptake. The blood flow is then calculated by dividing the oxygen uptake by the arteriovenous oxygen difference, which is the Fick equation for cardiac output. But to apply these data to the calculation of blood flow, a number of assumptions must be made, namely:

1. The pulmonary blood volume does not change during the period of measurement.

2. Direct utilization of oxygen by the lungs is negligible.

3. The concentrations of oxygen in the blood entering and that in the blood leaving the lungs are constant.

4. The blood samples obtained are truly representative of mixed venous or arterialized blood.

5. The rate of flow remains constant.

Obviously, the accuracy of the flow thus calculated will be related directly to the degree to which these conditions are fulfilled, i.e., to the "steady-state" maintained during measurement. When carefully applied, this direct Fick method of measuring blood flow is the best method currently available for the study of intact man.

The pulmonary circulation is normally a high flow, low pressure system. Since the lungs receive the entire output of the right ventricle, they have a greater blood flow than any other organ in the body. This inflow is augmented slightly by the bronchial arterial flow, most of which passes into the pulmonary veins. Since the pulmonary circulation is interposed between two pumps, the right and left ventricles, it is essential that, except for very transient conditions, the output of these two pumps must be identical to avoid any net change in pulmonary blood volume. It follows that the two pumps must be very delicately integrated and balanced to preserve the integrity of the pulmonary circulation.

Pressure

The vascular bed of the lung presents a resistance to blood flow which is only a fraction of the systemic resistance. Consequently, the pressures within the pulmonary arteries are only one-fifth to one-sixth of those found in the systemic arteries. There is considerable latitude in the normal "adult" pressure within the pulmonary artery, with a systolic range of 11 to 29 mm. Hg and a diastolic range of 4 to 13 mm. Hg.[9] Such pressure levels are attained as early as two weeks after birth and are often not higher after 66 years.[17, 29] However, during the first two weeks of life, higher pressures are observed, due to arteriovenous shunting of blood through the still patent ductus arteriosus[1, 25] and to incomplete regression of the thick medial smooth muscle of the muscular arteries carried over from fetal life.

It is not the pulmonary arterial pressure alone, but rather the pressure *gradient* from the pulmonary arteries to the left atrium, which impels blood through the pulmonary vascular bed. While the left atrial pressure has been measured directly in intact man using the various technics of left atrial needle puncture, it is more common to obtain a pulmonary arterial wedge pressure, employing a cardiac catheter introduced via the venous circulation. This technic, as described originally by Hellems,[14] often gives a reasonably accurate approximation of the left atrial pressure. Such "wedge" pressures must be interpreted with caution, however. If pulmonary venous constriction occurred, then the wedge pressure would reflect the elevated venous pressure, while the left atrial pressure remained normal. Lack of correlation between wedge pressure and left atrial pressure has also been reported in cases of mitral stenosis, when the left atrial pressure is abnormally elevated.[24] Nevertheless, the measurement of a reliable wedge pressure is generally

chiefly to the posterior pulmonary plexus situated on the ventral side of each lung root. The parasympathetic pulmonary fibers are branches of the vagi and also communicate with the posterior pulmonary plexus of each lung From each plexus, parasympathetic and sympathetic fibers are distributed together to the blood vessels, bronchi and glands of the lungs

The innervation of vascular structures within the lung varies in richness. Best supplied are the small bronchial arteries, while the pulmonary arteries are less richly innervated, and the pulmonary veins have a poor supply limited to their extrapulmonary parts and large intrapulmonary branches As in the systemic circulation, the pulmonary sympathetics transmit vasoconstrictor impulses, while the parasympathetics produce vasodilatation

Numerous investigators have described afferent nerve endings of various types in the walls of pulmonary arteries and veins, the latter especially near the junction with the left atrium These appear to be both baroreceptors and chemoreceptors concerned with reflex phenomena,[6, 29] including not only intrapulmonary circulatory adjustments but widespread systemic effects as well, e g , the Bezold-Jarisch reflex.

Physiology

To accomplish the lung's primary function of gas exchange, the pulmonary blood flow is spread into a thin sheet within the pulmonary capillary bed and thus is exposed to the alveolar air. This vast aerating surface has been estimated to be between 50 and 100 M², or about the size of a tennis court. The degree to which this blood is oxygenated is dependent on a number of factors, including the oxygen pressure gradient between the alveolar air and the capillary blood, the kinetics of hemoglobin and other chemical reactions, *the shape of the* hemoglobin dissociation curve at the existing blood pH, the permeability of the alveolar-capillary membrane, the rate of blood flow and the hemoglobin concentration The oxygenation of blood takes place with amazing rapidity. At rest, any given RBC is exposed to alveolar air for only ⅔ second, and during exercise, with the increased speed of circulation, this time may be cut in half. Yet, gaseous equilibrium can be closely approached in this short time, and with normal blood perfusing a normal pulmonary capillary bed, it is doubtful that blood can ever traverse the pulmonary capillaries so rapidly that there will be insufficient time for equilibrium to occur This is not true in pathologic states, wherein blood will reach the pulmonary veins less than fully saturated even though the partial pressure of oxygen in the alveoli is normal.

Distribution of Blood Flow

The distribution of blood flow through the lung is probably not uniform When an indicator substance is rapidly injected directly into the pulmonary artery, a concentration-time curve results whose shape suggests that there is a distribution of traversal times[22] This implies either that the velocity of blood flow is greater in some areas than in others or that the pathways followed by the blood are of different lengths While this spread of all traversal times is probably real, the *effective* traversal times may well be confined to a relatively narrow range This is suggested by the observation that the shape of an indicator-dilution curve, once established in the systemic venous system, is little altered by passage through the lungs[18]

The concept of the nonuniform distribution of blood flow through the lungs is compatible with diffusing capacity measurements reflecting the functional state of the capillary bed. All methods for measuring diffusing capacity show that this capacity normally increases considerably with exercise Since the increase cannot be explained simply on the basis of increased flow through a vasculature unchanged by exercise, it implies that the capillary bed is only partly perfused at rest and that, as flow increases with exercise, *this is accommodated by the opening* up of previously unperfused capillaries. How this is regulated is not known The pronounced effect of gravity on ventilation-perfusion relationships is another indication of the nonuniform distribution of the pulmonary blood flow.[21]

The technic of right heart catheterization, permitting direct access to the pulmonary arterial bed in intact man, has proven to be an

flowing through a tube 50 micra in diameter.[12] While these unusual properties of blood tend to reduce the influence of viscosity on the calculated vascular resistance, this does not mean that the marked increase in viscosity resulting from polycythemia is a negligible factor.

Through a rigid tube of fixed resistance, flow will bear a linear relationship to pressure, i.e., the ratio of pressure to flow, which defines resistance, will be a constant. Blood vessels are not rigid, but distensible, and hence the calculated vascular resistance is dependent on the pressure (and resultant flow) existing at the time of measurement. When the relationships of Poiseuille's equation are obeyed, then the *calculated resistance is inversely proportional* to the fourth power of the radius ($R \propto 1/r^4$). This means that a small increase in radius produces a proportionately much greater decrease in resistance. Thus, if the degree of vascular tone (constricting force) remains constant, a rise in pulmonary arterial pressure and hence an increase in transmural pressure (distending force), will produce an increase in blood vessel radius, which means a decrease in vascular resistance, and hence an increase in flow, indicating proportionately an excess of pressure. Furthermore, it is apparent that this phenomenon will be more manifest the more easily the vessel wall can be stretched. As the vessels become distended and reach the limit of their elasticity, they will behave more and more like rigid tubes. Considering specifically the pulmonary vascular bed, which is normally a low pressure system, the calculated vascular resistance will be highly dependent on transmural pressure at low pressures and will become progressively more independent as higher distending pressures are attained.

From these considerations, there emerges the important distinction between calculated vascular resistance and vascular tonus. Resistance considers only the *pressure gradient* across the vascular bed, whereas vascular tone considers the *transmural pressure* which tends to distend the vessels. Consider a pulmonary vascular bed through which flow remains constant and across which the pressure gradient remains constant. It follows that the calculated resistance will also be a constant. Under normal circumstances, the mean pulmonary arterial pressure may be 15 mm. Hg and with a given degree of vascular tone, a certain degree of distension would exist. If, however, due to mitral valve obstruction, the pulmonary venous and pulmonary arterial pressures are elevated, but the pressure gradient and flow remain unaltered, then there will be no change in calculated resistance. However, the pulmonary arterial distending pressure may now be increased threefold to 45 mm. Hg. Since the calculated resistance has not changed, this implies that no vasodilatation has resulted from the elevated pressures. This can be true only if the vascular tone has *increased* to balance the increased distending pressure and thus prevent an increase in radius. *Thus, calculated resistance is an index of blood vessel radius*, whereas distending pressure is an index of vascular tone.

The foregoing discussion is based on the assumption that the entire pulmonary vascular bed is analogous to a single tube whose resistance is varied by a change in radius. While it is true that resistance will decrease as vessel radius increases, it is also true that the opening of vessels previously closed completely will also reduce resistance. To distinguish between an increase in the number of patent vessels and a dilatation of vessels already open is most difficult.

In addition to normal vascular tone and blood viscosity, there are numerous other factors which can contribute to the total resistance to blood flow through the lung. An elevation in left atrial pressure can result from increased diastolic filling pressure of the left ventricle, incompetence of the mitral valve or a decrease in the area of the mitral valve, with the exaggerated effect of an increased heart rate and a shortening of ventricular diastole. A constriction may exist at the junction of the pulmonary veins with the left atrium, as in cor triatriata. The total cross sectional area of the pulmonary veins may be diminished by constriction or contraction.[8] A rise in airway pressure could either be transmitted to elevate the pulmonary capillary pressure or actually collapse a significant number of capillaries and thus reduce the total area of the capillary bed. Obviously, the resistance to flow would be increased by con-

agreed to reflect left atrial pressure and therefore to be of great value in determining the pulmonary vascular pressure gradient. Normally, this gradient is only 8 to 10 mm. Hg.

Vessel Size and Tone

The diameter of any given blood vessel will be determined by the balance between distending and constricting forces. One distending force is the difference in pressure between the lumen and the outside of the vessel, i.e., the transmural pressure. Since the pulmonary vessels are inside the chest, the external vascular pressure is the changing intrathoracic pressure. Obviously, this intrathoracic pressure as well as the intraluminal vascular pressure must be measured to determine the transmural pressure.

A second distending force exists as a consequence of the mechanical attachments between the pulmonary blood vessels and the other structures in the lung, so that as the lung expands, the large blood vessels literally may be pulled open.

Constricting forces are of two types. There is the passive recoil of stretched elastic and collagenous fibers within the vessel wall and surrounding lung tissue. In addition, there is the active contractile tone of the circular smooth muscle layer in the media.

Thus, if the transmural pressure decreases and the tone of the vessel wall remains unchanged, then the vessel will decrease in diameter. Conversely, if the transmural pressure remains constant, but the vascular smooth muscle relaxes, then the vessel will increase in diameter. These obvious facts must be kept in mind constantly when one is considering changes in pulmonary vascular resistance.

Resistance

Pulmonary vascular resistance is a calculated numerical factor obtained by dividing the pressure gradient across the pulmonary vascular bed by the pulmonary blood flow. In practice, the pressure gradient is obtained as the difference between the mean pulmonary arterial and wedge pressures, while the flow is determined simultaneously and most reliably by applying the direct Fick principle. Due to the potential errors inherent in each of these measurements, the calculated resistance is certainly not precise. Aside from these inaccuracies, the subsequent interpretation of "resistance," and even more, of a change in resistance, is a hazardous matter. Nonetheless, when cautiously applied, pulmonary vascular resistance is a valuable concept.

The interpretation of "resistance" usually begins with Poiseuille's law, which states that when a homogeneous Newtonian fluid is flowing at a constant rate through a single, straight, rigid tube of uniform dimensions, then

$$F = [\Delta P]\left[\frac{\pi}{8}\right]\left[\frac{1}{\eta}\right]\left[\frac{r^4}{L}\right]$$

F = flow

ΔP = pressure gradient.

η = viscosity

r = radius

L = length

It follows, then, that the resistance to flow, R, is defined by the expression,

$$R = \left[\frac{\Delta P}{F}\right] = \left[\frac{8}{\pi}\right][\eta]\left[\frac{L}{r^4}\right]$$

But in attempting to apply this exact mathematical expression to the pulmonary circulation, one realizes immediately that none of its specifications is fulfilled. Blood is not a homogeneous liquid, flow is not constant but pulsatile, the blood vessels curve and branch, tapering rather than cylindrical; they are elastic and change in both diameter and length, and pressures are both pulsatile and undulating. Obviously, therefore, one can speak in only very general terms when endeavoring to interpret pulmonary vascular resistance in terms of the Poiseuille equation.

Blood is not a homogeneous fluid, but rather a suspension of corpuscles of appreciable size in a fluid medium containing macromolecules of variable dissociation. The corpuscles manifest axial streaming at very low flow rates, which greatly reduces the effective viscosity of blood. Furthermore, the effective viscosity of blood decreases as the radius of the tube decreases. Because of this paradox, the effective viscosity of blood flowing through a vascular bed is the same as that measured with blood

vascular bed which will initiate or further the obstructive element and heighten the pulmonary vascular resistance.[35] Elevated pressure within a muscular structure will also tend to stimulate a vasoconstrictive response which may further decrease the cross-sectional area of the pulmonary vascular bed and further elevate the pulmonary artery resistance. At this point, we may analyze in more detail from a physiologic and structural standpoint these major mechanisms that give rise to production of pulmonary artery hypertension.

Elevation of Pulmonary Capillary Pressure

The elevation of pulmonary capillary pressure is almost always the result of obstruction to pulmonary venous blood flow This obstruction may be at any level from the left ventricle to the pulmonary veins The pulmonary capillary pressure may become slightly elevated in a normal individual under special circumstances, e g , during severe exercise or other conditions that result in greatly elevated pulmonary artery blood flows. Other experimental conditions would include the rapid intravenous injection of saline solution[7] or the use of a potent systemic vasoconstrictive substance such as noradrenaline [2]

Normal mean left atrial pressure, as usually measured, is between 5 and 9 mm Hg As the normal mean pulmonary artery pressure is in the vicinity of 13 to 18 mm. Hg, this results in a gradient of about 8 to 10 mm Hg across the pulmonary vascular bed *Any rise of pulmonary capillary pressure must of necessity result in a concomitant elevation of the pulmonary artery blood pressure,* if the normal pressure gradient and flow across the capillary bed are to be maintained. An increase in pulmonary capillary pressure is thus one of the mechanisms responsible for the genesis of pulmonary hypertension The pulmonary artery pressure is increased only to the extent of the capillary pressure elevation, and a normal gradient across the capillary bed may be maintained. As a physiologic mechanism, this has been termed passive pulmonary hypertension by Wood [34]

The pulmonary venous pressure elevation may at a certain point trigger a reflex mechanism that results in vasoconstriction at the pulmonary arteriolar level.[29] This would bring into play an increase in pulmonary vascular resistance and hence an additional mechanism in the resulting pulmonary hypertension. This reflex remains to be clearly established and will be discussed further at a later point.

Variations in intrapulmonary and intrathoracic pressure must be considered in relation to the elevation of pulmonary capillary pressure. Although probably rarely significant, it would seem feasible that an increase in alveolar pressure would be transmitted to the capillary bed and, if widespread, might affect the pulmonary artery pressure Variations in intrathoracic pressure may also effect the capillary pressure and thereby the pulmonary artery pressure, but this mechanism is probably unusual and of minor significance.

Let us, at this point, consider some of the conditions that are associated with obstruction to venous flow and thereby, in a retrograde and passive manner, elevate the pulmonary artery blood pressure

Increase in resistance to filling of the left ventricle. This may be secondary to an increase in residual diastolic blood volume due to failure of the left ventricle. This failure may be the result of an obstructive defect such as systemic hypertension or aortic valve disease, or it may be due to inadequacy of the myocardium secondary to coronary artery disease, or due to a primary myocardial fault such as infiltration with amyloid. Restriction of diastolic relaxation and the impedance of systolic ejection may also result in elevation of ventricular diastolic pressure Constrictive pericarditis, marked fibrosis of the myocardium and restrictive endocarditis are conditions that will effect this change These conditions rarely result in any considerable elevation of the pulmonary artery blood pressure The pulmonary artery systolic pressure is usually between 35 to 50 mm Hg in these conditions and the gradient across the capillary bed is normal, or but slightly increased.

Mitral valve disease and mitral stenosis. When the mitral valve orifice is decreased to a certain critical area, the left atrial pressure rises. As the left atrial-pulmonary venous-capillary system contains no valves, any rise in left atrial pressure is transmitted to and across the pul-

striction of the small muscular arteries and arterioles, and this would be more significant in the presence of hypertrophy of their muscular medial elements. In addition, intimal proliferation, thrombosis and complete obliteration can occur in these and larger arterial vessels.[8] The problem of interpreting an abnormal pulmonary resistance is further compounded by the effect of the total volume of blood within the pulmonary vascular bed. It is no wonder that critical investigators use this all-encompassing term, the "pulmonary vascular resistance," with reservations

Regulation

Since an investigation of factors which regulate the pulmonary circulation leads inevitably to the interpretation of changes in pulmonary vascular resistance, it is understandable why there is still much controversy in this field Furthermore, even the firm establishment of a definite regulatory mechanism often gives little indication of its functional significance

Anatomic studies indicate the presence of a complete autonomic reflex apparatus supplying the pulmonary vascular bed, and I deBurgh Daly[6] has produced very convincing evidence that reflexes involving the pulmonary circulation do indeed exist. Humoral factors, including norepinephrine,[2] acetylcholine[35] and serotonin,[30] all have direct actions on the pulmonary vasculature. In addition, other chemical agents with direct or reflex actions originating from the lung vessels include the normal blood gases, oxygen and carbon dioxide, and perhaps the pH of the blood itself. Also, the toxins produced by certain gram negative rods apparently cause constriction of the pulmonary veins Certain drugs have direct actions on vascular smooth muscle, e g , tolazoline, and thereby can alter pulmonary arteriolar resistance [10]

Auxiliary Functions

No review of the normal pulmonary circulation would be complete without some mention of the auxiliary functions, established or potential, attributed to this vascular bed. Certainly it can serve as a blood reservoir, playing a major role in the circulatory adjustments to changes in posture. Being interposed between the systemic venous and arterial systems, the pulmonary bed acts as a mechanical filter for venous emboli and bacteria. The lung also removes chemical substances from the venous blood by enzymatic action, e g , oxidizing serotonin and acetylcholine. Furthermore, the lung is rich in heparin and certain enzymes important in the blood-clotting mechanisms However, the significance of these materials being located in the lung is poorly understood

Pulmonary Hypertension

Thus far, the characteristics of the pulmonary circulation under normal conditions have been considered. However, this discussion would be incomplete if the factors responsible for the production of pulmonary hypertension were not also examined

The term pulmonary hypertension implies an elevation of the pulmonary artery pressure to levels above the accepted limits of normal, i e , above a figure of 30/12 mm Hg. Age may well have some effect on the pulmonary artery pressure, just as it frequently has on the systemic blood pressure. We have catheterized older patients with normal cardiovascular systems and in some have found the pulmonary artery pressure above the accepted limits of normal The maintenance of a physiologic pulmonary artery blood pressure is dependent on a normal relationship between the volume of pulmonary artery blood flow per unit of time and the resistance to that flow The most important and best understood of the factors responsible for elevation of pulmonary artery blood pressure are. (1) elevation of pulmonary capillary pressure, (2) decrease in over-all cross sectional area of the pulmonary vascular bed and (3) significant increase in pulmonary artery blood flow Pulmonary blood volume, viscosity of the blood, bronchiopulmonary artery anastomoses, intrapulmonary and intrathoracic pressure may all, at times, play some part in the development of pulmonary hypertension, although the mechanisms are less well known and probably of minor importance

Pulmonary hypertension may result from an aberration of any one of these mechanisms and, if of sufficient severity and duration, will produce pathologic changes within the pulmonary

will result in an increase in resistance to pulmonary blood flow. However, the remarkable distensibility of the pulmonary vessels provides a large compensatory reserve when the pulmonary vascular bed is only locally reduced. Thus, more than 50 per cent of the total lung volume must be removed before a significant rise in pulmonary arterial pressure results It is well established that patients with unilateral lung disease do not develop pulmonary hypertension following pneumonectomy when the remaining lung is normal. Recent work in animals involving selective lobectomy has suggested that the distensibility of the lower lobes may not be as great as that of the upper lobes. Hence, not only the volume (mass) of lung tissue removed, but also its anatomic location within the thorax, may be important in determining the resultant change in vascular resistance.

Pulmonary emboli. Pulmonary hypertension is frequently seen when there is widespread pathologic alteration of the pulmonary vascular bed. Obstruction and obliteration of vast numbers of small pulmonary arterial branches by miliary emboli or thromboses can so reduce the total pulmonary bed that severe pulmonary hypertension results In this situation, the remaining unobstructed blood vessels may be normal (or at least not primarily involved).

Medial hypertrophy Widespread narrowing of the small muscular pulmonary arteries, without a reduction in the total number of patent vessels, will also increase the vascular resistance to blood flow. Thickening of the walls of small muscular arteries due to medial hypertrophy will in itself reduce the vascular lumen. Constriction of these hypertrophied vessels can then produce a marked increase in vascular resistance "Arterial contracture" in the absence of medial hypertrophy has also been implicated in certain cases of pulmonary hypertension

Constriction of small muscular arteries with hypertrophied media accounts in part for the pulmonary hypertension normally seen in the immediate postnatal period. If regression of this medial hypertrophy does not occur in a normal fashion, as in certain patients with a ventricular septal defect or a patent ductus arteriosus, then an increased pulmonary vascular resistance will persist.[8, 13] The resultant pulmonary hypertension apparently traumatizes the pulmonary arteries, so that with the passage of time, intimal proliferation, fibrosis, thrombosis and atherosclerosis appear. These lesions also reduce the lumina of the small pulmonary vessels. Their effect is not always simply additive, however, for as the obstructive lesions increase in prevalence, there is a concomitant decrease in the extent of medial hypertrophy. Consequently, there may be little change in the magnitude of the increased pulmonary vascular resistance over long periods of time in these patients, even though the nature of the vascular obstruction is being altered

Regression of Vascular Changes

Vascular smooth muscle which has become hypertrophied from continual constriction is potentially capable of regressing to normal. Hence, pulmonary hypertension due to vasoconstriction is also potentially reversible. Acute reduction of a high pulmonary resistance can be produced in selected patients by the administration of the vasodilator, tolazoline.[10] This response is believed to be of value in predicting the reversibility of pulmonary hypertension following closure of a ventricular septal defect In older patients in whom obstructive pulmonary vascular lesions rather than medial hypertrophy predominate, tolazoline has little or no effect. The high pulmonary vascular resistance in these patients is presumably irreversible. However, only on the basis of actual experience in the next few years can the validity of these concepts be established.

The Genesis of Pulmonary Vasoconstriction

Hypoxia. While pulmonary vasoconstriction is an established phenomenon, the mechanisms involved are poorly understood. Alveolar hypoxia increases the pulmonary vascular resistance by means of vasoconstriction, but whether this is a neurogenic reflex or due to humoral or direct local effects is not known.[16] Neither is the anatomic site of the constriction established. Regardless of the mechanism, hypoxic vasoconstriction contributes significantly to the pulmonary hypertension in severe pulmonary emphysema Hypoxic vasoconstriction is also

monary bed and the pulmonary artery pressure is elevated accordingly. In mild degrees of mitral valve stenosis, the pulmonary hypertension may be purely passive in nature and a normal pressure gradient across the capillary bed is preserved However, the pulmonary artery pressure frequently rises out of proportion to the left atrial pressure when the stenosis is of such severity as to elevate the left atrial pressure to 25 mm Hg or more At this point, the rise in pulmonary artery pressure is in excess of a rise that can be accounted for on mere retrograde transmission, and the pressure gradient is increased This is believed to be the result of the development of an elevation in the pulmonary vascular resistance as an additive factor, with a further rise in the pulmonary artery pressure resulting This increase in the pulmonary vascular resistance has been stated to act as a "protective" mechanism, preventing sudden and marked elevation of the pulmonary capillary pressure and the resulting symptoms that would ensue

The mechanism responsible for this increase of the pulmonary vascular resistance is not entirely clear Some investigators consider this to be an active form of pulmonary hypertension and due to a reflex triggered by a critical level of the pulmonary venous pressure [29] It is rarely noted when the left atrial pressure is but slightly to moderately elevated, as with left ventricular failure or myocardial disease, giving rise to increased resistance to filling

Support for a reflex vasoconstrictive element to the pulmonary hypertension in the patient with severe mitral stenosis is the sudden and dramatic fall in pulmonary artery pressure that may be noted on recatheterization within a few weeks of successful mitral valvulotomy. The studies of Wood and others with acetylcholine would also suggest a vasoconstrictive element.[35] He has reported that, on injecting 1 mg. of acetylcholine into the pulmonary artery of patients having mitral stenosis with marked pulmonary hypertension, there follows a fall in pulmonary artery pressure and resistance and that the cardiac output rises as does the left atrial pressure The acetylcholine is inactivated within the lungs and there is no direct effect on the systemic circulation. In our own laboratory, we have noted a similar response following the intrapulmonary artery administration of tolazoline hydrochloride. Such studies, however, are not completely conclusive, though suggestive.

A recent study by Sanger and associates[29] would seem to add further evidence in support of the presence of a reflex vasoconstrictive mechanism In their experiments, the left lung was isolated from the pulmonary circulation, while the nerve pathways were left intact The pressure within the venous and capillary system of the isolated lung was raised to 35 to 45 mm. Hg. This pressure elevation resulted in a rise in the pulmonary artery pressure in the opposite lung The design of the experiment led to the conclusion that the pulmonary hypertension was the result of reflex arteriolar constriction When bilateral thoracic sympathectomy and transection of the pulmonary vagus branches preceded the experiment, pulmonary hypertension did not develop

It is also possible that no vasoconstrictive element need be postulated, but that the sudden and significant rise in pulmonary artery pressure occurs when the critical area of the pressure-volume curve of the pulmonary vascular bed is reached

Congenital defects involving stenosis of the pulmonary veins The genesis of the pulmonary hypertension developing under these circumstances is no different from that described under the previous heading of mitral stenosis

Any condition giving rise to obstruction of pulmonary venous blood flow results in structural changes within the pulmonary vascular bed that depend on the severity and duration of the obstruction. The pulmonary veins develop increased thickness of adventitia and intimal fibrosis. The small muscular arteries will show slight medial hypertrophy and intimal proliferation of varying degree Capillaries dilate and develop a thickened basement membrane, and macrophages containing hemosiderin may be noted in the alveoli.

Decrease in Over-all Cross Sectional Area of the Pulmonary Vascular Bed

Lobectomy A reduction in the total cross sectional area of the pulmonary vascular bed

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observed in residents of high altitudes, producing mild pulmonary hypertension in man, and severe pulmonary hypertension leading to right heart failure in cattle.[27]

Neurogenic reflex. Marked elevation of left atrial and pulmonary venous pressures produces precapillary vasoconstriction, as already mentioned.[29] Here, the mechanism appears to be a neurogenic reflex, since the response is abolished by denervation of both lungs.

Humoral. Serotonin is the most powerful pulmonary vasoconstrictor known. Some investigators believe that following pulmonary embolism, it is the release of serotonin which accounts for the marked increase in pulmonary vascular resistance.[30]

Local stretch reflex. Constriction of hypertrophied small muscular arteries in the lung elevates the pulmonary vascular resistance in some patients with intracardiac septal defects. When the systemic and pulmonary circulations are in direct communication through a large defect, then the high systemic pressure is transmitted directly into the pulmonary vascular bed. Distention of the pulmonary vessels stretches the smooth muscle coats. Such a stretch is the physiologic stimulus to produce contraction of smooth muscle. This contraction would narrow the vessels, increase their resistance and thereby sustain the high pressure. Through such a local stretch reflex, pulmonary hypertension would tend to be self perpetuating. Neurogenic vasoconstriction may also play a role in sustaining the elevated pulmonary vascular resistance in these patients. However, whether these or other mechanisms are actually important remains to be established.

Significant Increase in Pulmonary Artery Blood Flow

This rarely of itself is the cause of elevated pulmonary arterial blood pressure and probably never is the sole factor in the genesis of significant pulmonary hypertension. As previously mentioned, the normal pulmonary vascular bed is so capacious and dilatable that a great reserve exists and but rarely is the flow of such a magnitude as to give rise to a disproportion between the volume of the flow and the over-all cross sectional area of the pulmonary vascular bed. Treadmill exercise studies in normal individuals performed in our laboratory revealed that elevations of the cardiac output to levels of 16 to 18 L. per minute give rise to pulmonary artery systolic pressures of only 35 to 40 mm. Hg. Also, many patients with atrial septal defects have been catheterized in our laboratory and normal pulmonary arterial pressures determined in the presence of pulmonary blood flows of over 15 L. per minute. Thus, it is evident that the normal lung enjoys great reserve like many other organ systems in the body.

When significant pulmonary hypertension (systolic pressure above 50 mm. Hg) does exist in the presence of an elevated pulmonary artery blood flow, it is almost certain that there is coexisting a decrease in the cross sectional area of the pulmonary vascular bed. Under these circumstances, pulmonary hypertension results from the increase in pulmonary blood flow. This is the usual situation in patients with intracardiac septal defects and large left-to-right shunts who have significant increases in the pulmonary arterial blood pressure. The term hyperkinetic pulmonary hypertension has been used to describe this type of pressure elevation.

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Functional Capacity and Exercise Tolerance in Patients with Impaired Lung Function

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PATIENTS with lung disease are often quite incapacitated and may have a lower exercise tolerance than many patients with heart disease. The low functional capacity is often difficult to prove without objective methods, and the incapacitation of the patients with lung disease is, therefore, not always recognized. At the other extreme, some lung diseases influence the exercise tolerance only slightly, although the patients may exaggerate their symptoms because of insurance or other monetary interests Sometimes, the lungs themselves may be normal, the difficulty in breathing resulting from extrapulmonary causes

Comparatively simple examinations are sufficient in many cases for the evaluation of the functional capacity. Complicated cases require a more complete examination of respiratory function including an analysis of all the processes that contribute to the gas exchange. This should be done not only at rest but also during exercise, when the functions are stressed and the pathologic changes accentuated

Detection of Disturbed Respiratory Function

The various facets of respiratory function may be examined by various tests which may demonstrate the presence of one or more disturbances of function

Most of the ventilatory function tests are *not objective*, since they require the co-operation of the patients and are *not specific*, since they measure several functions simultaneously Examples of such tests used for the evaluation of the ventilatory function are: determination of lung volumes, including the residual volume, maximal voluntary ventilation (MVV), maximal flow rates and forced expiratory volumes Such tests usually will not detect slight pathologic changes.

Other function tests are more *specific* in that they measure essentially one function and at the same time are *objective* in that they are almost independent of the co-operation of the patient Examples of such tests for examining the ventilatory function are determination of *pulmonary compliance and resistance* as well as airway resistance to air flow [13]

For analysis of gas mixing in the lungs, the single breath nitrogen test[2] or the wash-in or *wash-out procedure with* H_2,[4] *He*[5] *or* N_2[17] are used They may be sensitive to small pathologic changes Gas exchange between alveolar air and blood is evaluated by the diffusing capacity *of the lungs as measured by* O_2 *or* CO methods.[19] Regulation of ventilation may be evaluated by the responses to inhalation of CO_2 gas mixtures, hypoxia or exercise

In the investigation of blood flow through the lungs it is possible to show the presence of a shunt (anatomic) by determination of the O_2 tension of arterial blood during 100 per cent O_2 *breathing*[3] This *test* is sensitive to small pathologic changes though it is not specific for shunts in the lungs. Uneven ventilation/blood flow relationships may be demonstrated by various methods[5a, 8, 33-35] and may also be deduced when there is a large "physiologic" dead space as compared to the "anatomic" dead space Increased pulmonary vascular resistance is assessed by the method of right heart catheterization

Unilateral lung function disturbances may be studied in several of the aforementioned aspects by bronchospirometry[25] or unilateral occlusion of one of the main branches of the pulmonary artery.[23]

The Use of Work Tests for Evaluation of Lung Function

Work test and lung function in normal subjects Evaluation of the total cardiopulmonary function is possible with the aid of work tests.

Chapter 13 of this book contains a description of a work test[27, 33] and its use in the evaluation of circulatory function. The application of this work test *in the evaluation of lung function* will be discussed here.

The work test, which is performed on a bicycle ergometer, consists of work with a stepwise increasing load. Each load is maintained for 6 minutes and the aim is to reach a final pulse rate of 150 to 170. In this form an advantage of the test is that it may be combined with the measurement of important respiratory parameters during periods of exercise at a relatively steady state. Such parameters include ventilation, O_2 uptake, arterial blood gas composition by oximetry[30] or direct analysis,[27] mechanical properties of the lungs[22] and diffusing capacity of the lungs.[25]

During exercise at a relatively steady-state using large muscle groups, such as in this type of work, lung function usually does not limit the O_2 uptake in normal subjects. This is evident from the fact that the O_2 tension of the arterial blood decreases comparatively little; thus, the O_2 saturation decreases insignificantly in normal subjects during exercise sufficiently strenuous to cause exhaustion and maximal pulse frequencies[27] (Fig. 1). Instead, the circulatory response (maximal pulse rate, stroke volumes and arteriovenous O_2 difference) at maximal work usually limits the O_2 uptake (Chapter 13). The stroke volume is the most important of these factors in determining the O_2 uptake and the working capacity,[26] since it shows the largest variation between individuals.

Work test and impaired respiratory function. In most patients, a work test of the type described can be carried out. The decrease in working capacity may be estimated quantitatively as the deviation from the normal relationship between the working capacity on the one hand and the total hemoglobin (THb), blood volume (or heart volume if no heart disease is present) on the other (see Chapter 13). Therefore, if the THb and blood volume are determined, it is possible to estimate how much an individual should be able to work. If the exercise tolerance, measured on the bicycle ergometer, is lower than the predicted value, the reason for the difference should be investigated.

Respiratory frequency as a sign of impaired lung function during the work test. Patients who develop a high pulse rate during the work test (170 beats per minute or more) may be regarded as limited primarily by circulation. The high pulse rate is also an objective sign that the work was close to maximal. The respiratory frequency is then usually less than 30 breaths per minute in normal subjects. Disturbed lung function may be suspected if the breathing frequency increases to more than 35 per minute. The pulse response to exercise may be approximately the same in normal and emphysematous subjects (Fig. 2), but the emphysematous subjects exhibit more rapid breathing frequencies at comparable work loads (Fig. 3). However, in heart disease, both the pulse rate and the breathing frequency increase abnormally during exercise.[39] These changes in pulse rate and breathing frequency are not diagnostic in themselves and must be interpreted in the light of other studies during the work test, or of lung function studies.

Many patients with severe pulmonary insufficiency do not develop high breathing frequencies during maximal work. Nor may a rapid breathing frequency during exercise be considered a valid sign of disturbed lung function, since this is common in patients who are either malingerers or who have pulmonary neurosis. Rapid breathing frequencies may also occur at times in healthy subjects and athletes. More specific lung function tests must then be employed to confirm or allay the suspicions.

The physical inactivity which may accompany chronic lung disease, particularly in combination with infection, may result in a reduction of the circulatory reserve. The total hemoglobin, blood volume and heart volume decrease, and a high pulse rate is reached at a lower load than before the disease.[35] Thus, in chronic lung diseases a high pulse rate may be reached at the same time or before the breathing frequency becomes high. This was well demonstrated in patients with chronic pulmonary tuberculosis.[11] In a study of 163 patients, all of whom had a low work capacity, 117 reached a high pulse rate (170 beats per min-

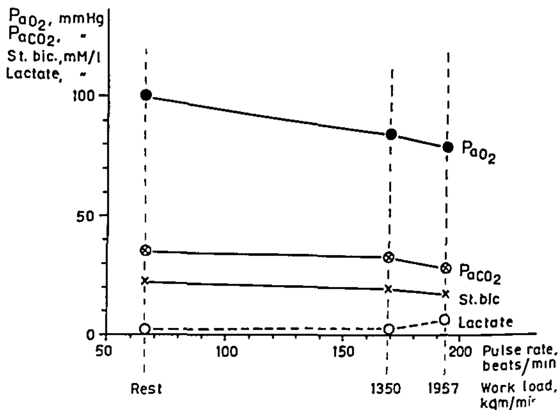


FIG 1 —Mean values from examinations on 14 young bicycle racers for Pa_{O_2}, Pa_{CO_2}, standard bicarbonate (St bic), and lactic acid (Lactate) in relation to pulse frequency and work load at rest, during heavy steady-state work and exhaustive work [37]

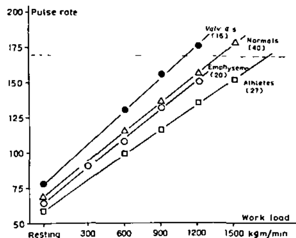


FIG 2 —Pulse rate in relation to work load on a bicycle ergometer in athletes (□), normal subjects (△), patients with emphysema (○), and valvular heart disease of slight degree (●)—all patients able to perform full occupational work [39] Numbers in parenthesis indicate the number of normal subjects or patients studied

ute) when the breathing frequency was still 30 or less. With a high degree of functional impairment of the lungs, high pulse rates may not be reached at maximal work.

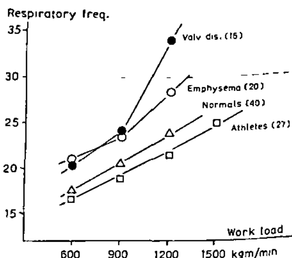


FIG 3 —Respiratory frequency in relation to work load in the same patients as in FIGURE 2 [39]

Factors beside impaired lung function which may limit exercise tolerance at a low pulse rate Several factors other than highly impaired lung function may limit the response of the pulse rate to exercise and lead to a false interpretation if the entire problem is not considered. Disease of the myocardium, such as

myocarditis or coronary insufficiency, may cause a low maximal pulse rate. This can often be recognized if an electrocardiogram is recorded during and after the work test[2] (Chapter 13) Muscular insufficiency may limit O_2 uptake and is recognized by the occurrence of leg pains during the exercise. Such instances are usually accompanied by high blood lactic acid concentrations.[10] Right-to-left shunts in the heart or central vessels may result in increasing hypoxemia and a limited rise in pulse rate. Finally, poor patient co-operation can result in a poor performance of the work test and is sometimes difficult to detect.

Evaluation of Respiratory Functional Capacity for Gas Exchange

As has been pointed out, the work test may be altered by several factors, and proper evaluation of the results of work tests requires the careful consideration of other respiratory function studies The presence of both heart and lung disease in the same patient particularly calls for more detailed evaluation

Tracing the course of oxygen transport through the cardiopulmonary system can be an aid in this evaluation. Oxygen transport may be limited by (1) impaired ventilation, (2) impaired diffusion or (3) impaired pulmonary blood flow The relationship between these main links in the chain of O_2 transport mechanisms may be expressed by the following equations, which are valid under steady state conditions.

$$\dot{V}_{O_2} = \underbrace{\dot{V}_A(P_{I_{O_2}} - P_{A_{O_2}})/P_B - 47)}_{\text{Alveolar Ventilation}} = \underbrace{D_{L_{O_2}}(P_{A_{O_2}} - \bar{P}c_{O_2})}_{\text{Diffusion}}$$

$$= \overbrace{\underbrace{(pf \times \text{stroke volume})}_{\dot{Q}} \times (Ca_{O_2} - C\bar{v}_{O_2})}^{\text{Blood flow}}*$$

The equations tell us that to maintain a certain O_2 transport, $\dot{V}_{O_2}$, the O_2 partial pressure difference between inspired and alveolar air, $P_{I_{O_2}} - P_{A_{O_2}}$, must be larger if the alveolar ventilation is insufficient; or the mean alveolar-capillary partial pressure difference, $\bar{P}_{A_{O_2}} - {}_{c_{O_2}}\bar{P}$, must be large when the diffusing capacity for the lungs for oxygen, $D_{L_{O_2}}$, is small; or the arteriovenous O_2 difference, $Ca_{O_2} - C\bar{v}_{O_2}$, must be large when the cardiac output, $\dot{Q}$, is small in relation of $\dot{V}_{O_2}$.

An impaired O_2 transport capacity in one of the transport mechanisms thus results in an increased concentration or partial pressure difference corresponding to the impaired function, and the O_2 gradients corresponding to the other mechanisms are often compensatorily decreased.

This simplified concept of the total picture of oxygen transport does neglect O_2 partial pressure differences between alveolar air and arterial blood due to uneven ventilation-perfusion relationships or shunts, but these will be discussed later.

Ventilatory Impairment

Impaired ventilation is the most common form of disturbed lung function. Signs that ventilation limits work capacity and O_2 up-

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* The symbols used in this chapter and their definitions are as follows:

pf = pulse frequency, beats per minute.
rf = respiratory frequency, breaths per minute
Ca_{O_2}, $C\bar{v}_{O_2}$ = O_2 content of arterial and mixed venous blood, respectively, ml /l.
$D_{L_{O_2}}$, $D_{L_{CO}}$ = diffusing capacity of the lungs for O_2 and CO, respectively, ml / min /mm Hg.
MVV = maximal voluntary ventilation (free rate) of maximal breathing capacity.

Gas Partial Pressures, mm Hg

$P_{A_{O_2}}$ = alveolar air ("effective") O_2 pressure.
Pa_{O_2}, Pa_{CO_2} = arterial O_2 and CO_2 tension, respectively
$\bar{P}c_{O_2}$ = pulmonary capillary mean O_2 tension
$P_{I_{O_2}}$ = O_2 pressure of inspired air (BTPS)

Gas Volumes Per Unit of Time

$\dot{V}_A$ = alveolar ventilation, l (BTPS)/min
$\dot{V}_D$ = dead space ventilation, l (BTPS)/min
$\dot{V}_E$ = expired minute ventilation, l (BTPS)/min
$\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ = O_2 uptake and CO excretion, respectively, ml (STPD)/min.

Other Symbols

$\dot{Q}$ = cardiac output, l/min
R = respiratory coefficient, $\dot{V}_{CO_2}/\dot{V}_{O_2}$
THb = total amount of hemoglobin, Gm.

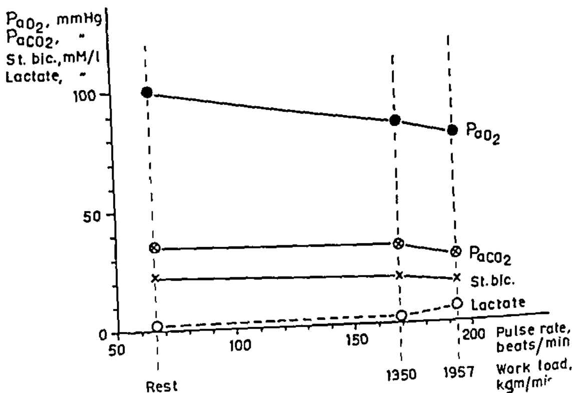


FIG 1—Mean values from examinations on 14 young bicycle racers for Pa_{O_2}, Pa_{CO_2}, standard bicarbonate (St bic), and lactic acid (Lactate) in relation to pulse frequency and work load at rest, during heavy steady-state work and exhaustive work [37]

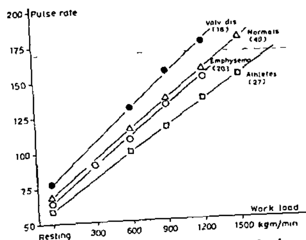


FIG 2—Pulse rate in relation to work load on a bicycle ergometer in athletes (□), normal subjects (△), patients with emphysema (○), and valvular disease of slight degree (●)—all patients able ... pa- or

patients studied.

ute) when the breathing frequency was still 30 or less. With a high degree of functional impairment of the lungs, high pulse rates may not be ... normal work.

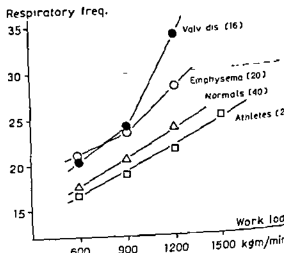


FIG 3.—Respiratory frequency in relation to w load in the same patients as in FIGURE 2 [38]

Factors beside impaired lung function w may limit exercise tolerance at a low pulse Several factors other than highly impa lung function may limit the response of pulse rate to exercise and lead to a false in pretation if the entire problem is not sidered Disease of the myocardium, suc

TABLE 1 —*Gas Exchange, D_{LCO}, and O_2 Gradients at Rest and During Exercise in Cases 1 to 5*
D_{LCO} was Determined by the Steady State CO Method.[33] The work performed by cases 2-4 was close to their maximal work capacity

	pf	rf	V_E	V_A/V_E	V_{O_2}	$\dot{V}_{CO_2}$	P_{AO_2}	P_{aO_2}	S_{aO_2}	P_{aCO_2}	D_{LCO}	$P_{IO_2} - P_{AO}$	$P_{AO_2} - \bar{P}_{cO_2}$	$P_{AO_2} - P_{aO_2}$ breathing 100% O_2
Case 1														
at rest	81	12	9 9	0 58	310	265	104	105	98	40	31	43	8	81
900 Kgm /min.	131	22	46.8	0 81	2240	1908	101	72	94	42	53	47	35	
at estimated maximal work													51	
Case 2														
at rest	80	14	9 9	0 47	254	246	100	78	—	46	8.6	46	24	162
100 Kgm /min	112	26	23 1	0 45	687	685	91	53	—	56	14 6	55	38	
Case 3														
at rest	80	17	12 4	0.53	273	247	115	38	—	33	4.3	34	52	205
200 Kgm /min.	138	28	44 2	0 64	842	806	124	20	—	25	8 7	25	79	
Case 4														
at rest	80	7	10 6	0 61	276	242	112	65	92	33	16 4	30	14	139
22,100 Kgm /min.	131	16	38 5	0.55	786	727	117	105	97	30	22 6	25	28	
Case 5														
at rest	107	11	4 9	0 47	216	171	74	57-59	85	64	25.1	76	7	223
600 Kgm /min	144	20	22.2	0 81	1515	1373	81	51	78	65	28 1	69	43	

For explanation of symbols, see footnote pp 651 and 652.

TABLE 2 —*Some General Characteristics of the Patients Described*

	Case 1 Normal Subject	Case 2 Emphysema	Case 3 Small D_L	Case 4 Thromboembolism of Pulm Art	Case 5 Hypovent Syndrome	Case 6 Respiratory Neurosis	
						1st Exam	2nd Exam
Age (yr)	18	60	38	42	45	43	
Height (cm)	184	176	179	171	177	178	
Weigh (Kgm)	63	72	70	88	84	96	
Work capacity (Kgm./min)	1500	c a 100	c a 250	c a 200	900	>600	
Work capacity % of predicted	104	11	18	13	45		
Heart volume, ml	870	—	760	1560	1160		
Total amount of hemoglobin (THb, g)	910	665	890	950	1210		
Blood volume, 1	7 0	4 9	5 9	6 4	6.5		
Hemoglobin conc Gm /100 ml.	12 9	13.7	15 2	11.1	17 5		
ECG at rest and during work	normal	VES	normal	R V. hypertrophy	normal	normal	
Lung volumes, 1 (BTPS):							
Vital capacity, VC	5 7	2 6	4 4	3.4	3 5	1.2	0 7
Funct residual capacity, FRC	4 1	6.2	3.2	2 8	2 0	3.3	3.5
Residual volume, RV	2 1	5 6	1 8	1.6	1 3	2.7	3 4
Total lung capacity, TLC	7 8	8 2	6 2	5 0	4 8	4.0	4.1
Gas mixing (Helium)	normal	delayed	normal	normal	normal	normal	normal
MVV, 1 (BTPS)/min.	140	31	97	114	106	34	47

take are: (1) The maximum voluntary ventilation (MVV) at free rate is about the same as the ventilation during the heaviest work performed in a work test, i.e., $\dot{V}_E/MVV_F$ approaches unity[29] MVV_F is not an objective measure, however, and a more objective sign appears to be that (2) the partial pressure of CO_2 in the arterial blood may be high even at rest or may increase during exercise At the same time (3) the partial pressure difference or O_2 between the inspired air and the alveolar air becomes larger than normal and the O_2 tension of the arterial blood, Pa_{O_2}, decreases during exercise The sampling of arterial blood during exercise is not difficult if polyethylene catheters are used.[27] (4) Ventilation often exceeds the normal in relation to the O_2 uptake or to the work load, indicating a large dead space ventilation if, at the same time, Pa_{CO_2} is normal or high The working capacity and O_2 uptake are then limited to what is compatible with the alveolar ventilation corresponding to the maximal total ventilation. This alveolar ventilation may be estimated if the ratio $\dot{V}_A/\dot{V}_E$ is known[32]; in patients with emphysema this is usually almost the same at rest and during exercise (TABLE 2).

These signs may be summarized in a diagram as in FIGURE 4. It is also quite useful in evaluating other types of respiratory disturbances than those of ventilatory insufficiency (see below) For comparison, the results from a normal subject (Case 1) are included in the diagram (see also TABLES 1 AND 2)

Impaired ventilation is exemplified by one patient with emphysema (Case 2) who was chosen because some difficulty was encountered in deciding if heart or lung insufficiency predominated He could only perform a small amount of work, and at the work test neither a high pulse rate nor a high respiratory rate was reached He worked 100 Kgm per minute for 6 minutes with a final pulse rate of 112 and breathing frequency of 26 per minute Under the next load, 200 Kgm per minute, he could continue for only about 2 minutes Heart volume, THb and blood volume indi-

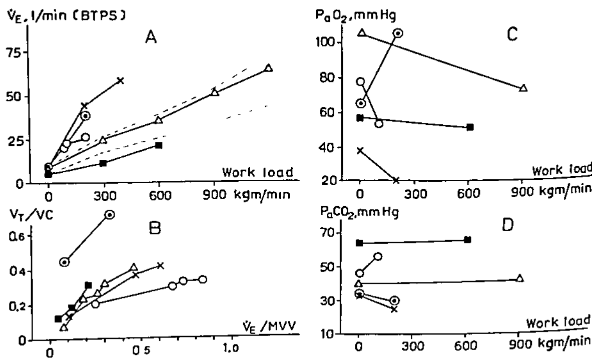


FIG 4 —Diagram showing conditions at rest and during exercise in a normal subject, case 1 (△), and in patients with various types of respiratory disorders (Cases 2 to 5) Case 2 has pulmonary emphysema with impaired ventilation (O); Case 3 has alveolar-capillary block (×)· Case 4 is a patient with thrombo-embolism of the pulmonary artery with impaired circu- [illegible] on, V_E, in [illegible] subjects) [illegible] oad, corre- sponding to the values in A. (C and D) Pa_{O_2} and Pa_{CO_2} [illegible]

TABLE 1.—*Gas Exchange, $D_{L_{CO}}$, and O_2 Gradients at Rest and During Exercise in Cases 1 to 5.* $D_{L_{CO}}$ was Determined by the Steady State CO Method [33] *The work performed by cases 2–4 was close to their maximal work capacity*

	pf	rf	$\dot V_E$	$\dot V_A/\dot V_E$	$\dot V_{O_2}$	$\dot V_{CO_2}$	$P_{A_{O_2}}$	$P_{a_{O_2}}$	$S_{a_{O_2}}$	$P_{a_{CO_2}}$	$D_{L_{CO}}$	$P_{I_{O_2}} - P_{A_O}$	$P_{A_{O_2}} - \bar P_{c_{O_2}}$	$P_{A_{O_2}} - P_{a_{O_2}}$ breathing 100% O_2
Case 1														
at rest	84	12	9.9	0.58	310	265	104	105	98	40	31	43	8	81
900 Kgm /min.	134	22	46.8	0 84	2240	1908	101	72	94	42	53	47	35	
at estimated maximal work													51	
Case 2														
at rest	80	14	9.9	0 47	254	216	100	78	—	46	8 6	46	24	162
100 Kgm /min.	112	26	23.1	0 45	657	685	91	53	—	56	14.6	55	38	
Case 3														
at rest	80	17	12.4	0.53	273	247	115	38	—	33	4 3	34	52	205
200 Kgm /min.	138	28	44.2	0 64	842	806	121	20	—	25	8 7	25	79	
Case 4														
at rest	80	7	10 6	0.61	276	242	112	65	92	33	16.4	30	14	139
22,100 Kgm /min.	134	16	38.5	0.55	786	727	117	105	97	30	22 6	25	28	
Case 5														
at rest	107	11	4 9	0 47	216	171	74	57–59	85	64	25 1	76	7	223
600 Kgm /min	144	20	22 2	0 81	1515	1373	81	51	78	65	28 1	69	43	

For explanation of symbols, see footnote pp 651 and 652.

TABLE 2 —*Some General Characteristics of the Patients Described*

	Case 1 Normal Subject	Case 2 Emphysema	Case 3 Small D_L	Case 4 Thromboembolism of Pulm Art.	Case 5 Hypovent Syndrome	Case 6 Respiratory Neurosis	
						1st Exam	2nd Exam.
Age (yr)	18	60	38	42	45	43	
Height (cm)	184	176	179	171	177	178	
Weigh (Kgm)	63	72	70	88	84	96	
Work capacity (Kgm /min.)	1500	c a 100	c a 250	c a 200	900	>600	
Work capacity % of predicted	104	11	18	13	45		
Heart volume, ml	870	—	760	1560	1160		
Total amount of hemoglobin (THb, g)	910	665	890	980	1240		
Blood volume, l	7 0	4 9	5 9	6 4	6.5		
Hemoglobin conc. Gm /100 ml.	12.9	13.7	15 2	11.1	17.5		
ECG at rest and during work	normal	VES	normal	R V. hypertrophy	normal	normal	
Lung volumes, l (BTPS):							
Vital capacity, VC	5.7	2 6	4 4	3 4	3 5	1 2	0 7
Funct residual capacity, FRC	4 1	6 2	3 2	2.8	2 0	3 3	3 5
Residual volume, RV	2 1	5 6	1.8	1.6	1.3	2 7	3 4
Total lung capacity, TLC	7 8	8 2	6.2	5 0	4.8	4 0	4.1
Gas mixing (Helium)	normal	delayed	normal	normal	normal	normal	normal
MVV, l (BTPS)/min	140	31	97	114	106	34	47

take are: (1) The maximum voluntary ventilation (MVV) *at free rate is about the same as* the ventilation during the heaviest work performed in a work test, i.e., V_F/MVV_F approaches unity.[29] MVV_F is not an objective measure, however, and a more objective sign appears to be that (2) the partial pressure of CO_2 in the arterial blood may be high even at rest or may increase during exercise. At the same time (3) the partial pressure difference or O_2 between the inspired air and the alveolar air becomes larger than normal and the O_2 tension of the arterial blood, Pa_{O_2}, decreases during exercise. The sampling of arterial blood *during exercise is not difficult if polyethylene* catheters are used.[27] (4) Ventilation often exceeds the normal in relation to the O_2 uptake or to the work load, indicating a large dead space ventilation if, at the same time, Pa_{CO_2} is normal or high. The working capacity and O_2 uptake are then limited to what is compatible with the alveolar ventilation corresponding to the maximal total ventilation. This alveolar *ventilation may be estimated if the ratio* $\dot{V}_A/V_t$ is known[32]; in patients with emphysema this is usually almost the same at rest and during exercise (TABLE 2).

These signs may be summarized in a diagram as in FIGURE 4. It is also quite useful in evaluating other types of respiratory disturbances than those of ventilatory insufficiency (see below). For comparison, the results from a normal subject (Case 1) are included in the diagram (see also TABLES 1 AND 2).

Impaired ventilation is exemplified by one patient with emphysema (Case 2) who was chosen because some difficulty was encountered in deciding if heart or lung insufficiency predominated. He could only perform a small amount of work, and at the work ... high respiratory

frequency of 26 per minute. *Under the next load*, ... Kgm per minute, he could continue for only about 2 minutes. Heart volume, THb and blood volume indi-

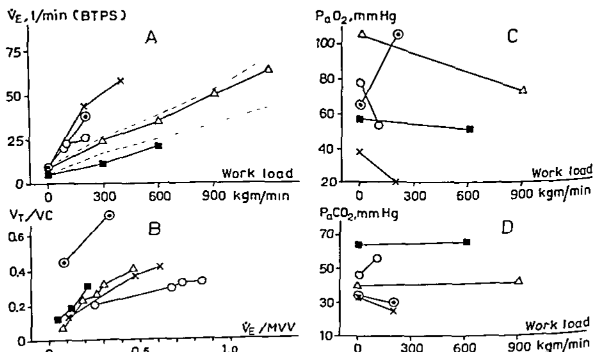


FIG. 4.—Diagram showing conditions at rest and during exercise in a normal subject, case 1 ... types of respiratory disorders (Cases 2 to 5). Case 2 has ... eolar-capillary block ... with impaired circu- ... Ventilation, V_E, in ... subjects). ... oad, corre-

Shepard[30] obtained similar results. Most normal subjects and most patients with cardiopulmonary functional disturbances do not reach this high mean alveolar-capillary P_{O_2} difference at maximal work. They may, therefore, be considered to have a "diffusing capacity reserve," and the O_2 uptake is not limited by diffusion (FIG. 5).

Further signs of limitation of working capacity by pulmonary diffusion are (3) decreasing O_2 saturation during exercise in spite of a low Pa_{O_2} and (4) an appreciable increase in working capacity when 100 per cent O_2 is inhaled.

Pulmonary diffusion as a limiting factor for the O_2 uptake is exemplified by Case 3 in TABLES 1 and 2 and FIGURE 4. This case exhibited a low diffusing capacity ("alveolar-capillary block"), but the other values are similar to those for the normal subject (Case 1). Case 3 with the low diffusing capacity had pulmonary changes, but these were not striking on the roentgenogram. The working capacity was low but a high pulse rate was not reached. This patient achieved a work load of 200 Kgm per minute for 6 minutes with a pulse rate of 116 and a respiratory rate of 28 per minute, but could work for only 2 minutes at 300 Kgm per minute and was then extremely cyanotic. The lung volumes and MVV were within the normal range, and there were no signs of ventilatory insufficiency. During exercise under a load of 200 Kgm per minute and with a ventilation equal to that of the normal subject at a load of 900 Kgm per minute, he could not maintain normal saturation of the arterial blood in spite of the low Pa_{CO_2}. Only a moderate shunt was indicated by the $P_{A_{O_2}} - \bar{P}c_{O_2}$ difference during breathing of 100 per cent O_2. The low D_L explains his functional insufficiency and limits his O_2 uptake to about 800 ml per minute or his working capacity to about 250 Kgm per minute, if normal working efficiency is assumed.

Impaired Circulation

Impaired circulation due to changes in the pulmonary vessels is probably more common than is generally recognized. Vascular changes in the lungs may limit O_2 transport in two ways: (1) The pulmonary vascular resistance may be high and limit the cardiac output. This may occur in patients with primary pulmonary hypertension or thrombo-embolism of the pulmonary artery.[31] The circulatory limitation of this type has much in common with the circulatory insufficiency of extrapulmonary origin, such as mitral stenosis. (2) There may be venous admixture to the arterial blood due to shunt or

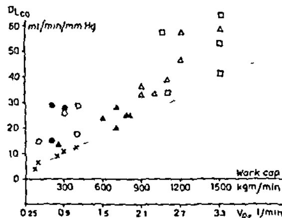


FIG. 5—Diffusing capacity of the lungs for CO ($D_{L_{CO}}$) measured at a pulse rate of 140 beats per minute in relation to work capacity (at pulse 170) and the corresponding O_2 uptake ($\dot{V}_{O_2}$). Patients with pneumonectomy are indicated by a solid triangle (▲) and those with mitral stenosis by a solid circle (●). Other symbols are as in FIGURES 2 to 4. In patients with lung disease, whose level of work allowed only low pulse rates (limitation of O_2 uptake by lung function), the work capacity and the corresponding V_{O_2} were taken as corresponding to the highest work load the patients managed to perform for 4 minutes. D_L was measured at a slightly lower load. The ratio $V_{O_2}/1.23 \cdot D_{L_{CO}}$ is the mean alveolar-capillary O_2 tension difference, $P_{A_{O_2}} - \bar{P}c_{O_2}$, at maximal work,[23] and the straight line corresponds to such a difference of 70 mm. Such a high value seems to be reached only when D_L limits the O_2 uptake. (Figure taken from ref. 29.)

uneven ventilation-perfusion relationships. The decreased O_2 saturation of arterial blood diminishes the maximum possible arteriovenous O_2 difference.

Signs that the circulation limits the O_2 transport and working capacity in cases of lung disease are:

1. A high pulmonary vascular resistance with pulmonary hypertension of such severity that it results in a small cardiac stroke volume. The stroke volume may be quantitatively related to the working capacity in these cases in the same way as in normal subjects or in patients with mitral stenosis (FIG. 6).[25, 26] Even if the pulse rate during the work test does not reach high values, which often seems to be the case in these patients, it is thus possible to get an objective and satisfactory quantitative measure of their maximal working capacity.

A high pulmonary vascular resistance limiting the working capacity is exemplified by a patient (Case 4)

cated circulatory dimensions compatible with a larger working capacity, but the electrocardiogram showed ventricular extrasystoles indicating the possibility of myocardial disease, as seen in TABLE 1

The lung volumes were of the type found in emphysema, and mixing of helium in the lungs was delayed The MVV was low, and the ventilation during exercise approached the MVV (FIG 4) The low Pa_{O_2} and the high Pa_{CO_2} even at rest indicated insufficient lung function, particularly since the changes were accentuated during exercise The ventilation was large in relation to the work load (FIG 4A), and the alveolar ventilation was small in comparison with the total ventilation (TABLE 2) *Disturbance of respiratory regulation* must be considered as a possible cause of the changes in alveolar ventilation and in the gas tension of arterial blood Some other features make it possible, however, to differentiate such a state from the mechanical type of ventilation insufficiency described here (see Case 6 below)

The maximal working capacity and the maximal O_2 uptake were estimated from the MVV and the fraction $\dot{V}_A/\dot{V}_E$ It was assumed that the maximal ventilation during exercise equalled MVV The maximal $\dot{V}_A$ and the corresponding $\dot{V}_{O_2}$ was then obtained from the equation

$$\dot{V}_{O_2}\max = \frac{(\dot{V}_A\ max)(Pa_{CO_2})}{0.863\ R}$$

$$where\ \dot{V}_A\ max \approx \frac{(MVV)(\dot{V}_A)}{\dot{V}_E}$$

If we take Pa_{CO_2} to be within the limits 46 to 56 mm Hg, the maximal $\dot{V}_{O_2}$ in case 2 would be 650 to 910 ml per minute This O_2 uptake with the low working efficiency (probably to some extent due to the high O_2 cost of breathing) would correspond to a working capacity of 100–200 Kgm per minute

In patients in whom it is desirable to get more objective evidence that the ventilation approaches the true maximal value, it is possible with an esophageal balloon to measure the intrathoracic pressure variations during exercise as well as during the performance of the MVV. Negative esophageal pressure swings of −20 to −50 cm. H_2O or more strongly suggest an almost maximal ventilatory effort.[31] Such values may be reached without exercise during acute attacks of bronchial asthma.

The mechanical properties of the lungs (lung compliance, and resistance, and airway resistance at defined lung volumes[6]) provide objective signs of the disturbed lung function in emphysema (as in most ventilatory insufficiencies), but they are not adequate for quantitating the degree of ventilatory insufficiency. The mechanical properties of the thoracic wall and particularly the state of the respiratory muscles are also important to the ventilatory function.[18]

In the emphysema patient (Case 2) other respiratory functions than ventilation did not seem to limit gas exchange *The diffusing capacity of the lungs*, D_{LCO} (steady state method) was reduced, but even with the maximal work, the calculated mean alveolar-capillary O_2 tension difference was small; thus, impaired diffusion should not have limited O_2 uptake[22] Although cardiac function was not evaluated during exercise by heart catheterization, it seems likely that cardiac function could meet the needs for the limited oxygen transport that ventilation permitted in this case

Cor pulmonale with increased pulmonary vascular resistance is known to develop when hypoxemia and hypercapnia are present at rest This may occur even without pathologic changes in the lungs in various hypoventilation states where the patients exhibit decreased *mobility of the chest wall and diaphragm*[15, 18] because of paralysis of respiratory muscles, kyphoscoliosis,[17] obesity with the Pickwickian syndrome[1, 7, 9, 15] and also because of disturbed respiratory regulation[21] *Cardiac function* should, therefore, be considered in cases of impaired ventilation

Impaired Diffusion

Impaired diffusion is less common Signs which suggest that diffusion limits the oxygen uptake and working capacity are (1) a small diffusing capacity of the lungs (which should be measured during exercise) and (2) a large mean alveolar-capillary P_{O_2} difference which increases during exercise when the O_2 uptake increases

The relationship between these factors is described by the equation:

$$P_{A_{O_2}} - \bar{P}c_{O_2} = \dot{V}_{O_2}/D_{L_{O_2}}$$

D_L was measured by the steady state *CO* method and it was assumed that $D_{L_{O_2}} = 1.23$ D_{LCO} It was found that when one breathes air at sea level, $P_{A_{O_2}} - \bar{P}c_{O_2}$ approached 70 mm. Hg at maximal work when diffusion was the limiting factor for the O_2 uptake.[29] With another approach and using other methods,

larger than the ventilation at the maximal work performed (TABLE 1). His ventilation during exercise was small as compared with the O_2 uptake and work load (FIG 4 AND TABLE 2) A shunt was not present as shown by the low $P_{AO_2} - Pa_{O_2}$ during 100 per cent oxygen breathing, nor was the arterial hypoxemia (at least at rest) caused by impaired diffusion

The primary disease in this patient was probably an epidemic encephalitis, which damaged the chemoreceptors of the respiratory center. The hypoventilation and arterial hypoxemia presumably caused a secondary polycythemia and large blood and heart volumes The abnormal blood gases seem to have induced an increased pulmonary vascular resistance, which disappeared following hyperventilation or 100 per cent O_2 breathing

Respiratory neurosis, simulation and aggravation may give other forms of disturbed ventilation, which seem to have a psychologic explanation. These forms are often found among insurance cases, social cases or patients with occupational diseases. They may be difficult to recognize without careful analysis Since the functional evaluation of these patients is often particularly important, and since they have many features in common, a description of their way of performing several function tests will be included

In performing the work test, these patients often stop working at a low work load when the pulse rate is still low The breathing frequency is usually high but often increases irregularly with the work load (being often highest with the first work load) The reaction during the work test thus may raise the suspicion of impaired lung function. Respiratory and other muscle groups are often tense, but the diaphragm moves normally when examined fluoroscopically. The VC is often small, the RV large, particularly in relation to TLC, and the MVV is small If the examinations are repeated, the results often differ on different occasions. Some patients require repeated tests to insure good co-operation and proper evaluation of function.

If the work test is combined with oximetry or analysis of arterial blood, both the oxygen saturation and the Pa_{CO_2} are within the normal range even for the heaviest work these patients perform Other more objective tests may or may not show disturbed lung function, depending on whether organic disease is also present

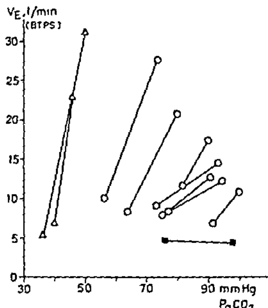


FIG 7 —Ventilation in relation to Pa_{CO_2} during breathing of 100 per cent O_2 and 5 to 7 per cent CO_2 in O_2 The ventilatory response to CO_2 in Case 5 (■) is compared with that in 7 patients with emphysema (O), with a Pa_{CO_2} during breathing 100 per cent O_2 of similar magnitude to that in Case 5 and with that in two normal subjects (Δ) (Figure taken from ref 21)

There is usually no difficulty in demonstrating by objective tests the absence of functional disturbances of the lungs Sometimes, a question remains about the mechanical properties of the chest wall as a possible factor limiting ventilation Measurement of chest wall compliance under general anesthesia may be a possible means of obtaining an objective measure of this factor

The greatest difficulty is the proper evaluation of total function in patients who have pathologic changes in lung function combined with their psychologic difficulties A disturbed gas distribution in the lungs, for instance, may be present without significant effects on total function

An analysis of the links in the chain of O_2 transport during exercise combined with pressure on the patient to increase his effort in the work tests, when no factor limiting further increase in the O_2 uptake is present, will lead in most cases to a proper estimate of the functional capacity of the patient. Such function tests also serve as a good starting point in the rehabilitation and training of such patients.

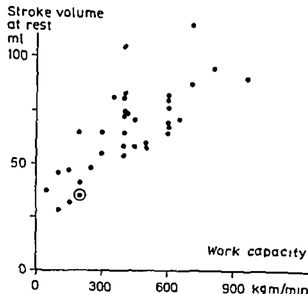


FIG 6 —Stroke volume at rest in relation to work capacity in patients with mitral stenosis[15] and the patient with thrombo-embolism of the pulmonary artery (Case 4) Two of the patients with flutter during the examination were not included There is an obvious positive correlation between the stroke volume and work capacity, but the variation is rather large This is to be expected as the stroke volume in these cases usually decreases during exercise, and the adaptation of the peripheral circulation (degree of blood O utilization) may be quite variable A better *relationship is obtained if* the stroke volume is measured during exercise (see Chapter 13) There seems to be a work capacity for a given stroke volume, however, which cannot be surpassed Symbols as in FIGURES 4 AND 5

with thrombo-embolism of the pulmonary artery [16] He had a low working capacity and a large heart volume in relation to THb and blood volume and electrocardiographic changes indicating right ventricular hypertrophy During the work test he stopped working at a low pulse rate (134 beats per minute) and a low respiratory frequency (16 respirations per minute) at 200 Kgm per minute load His MVV and vital capacity were within the normal

low Pa_{CO_2} (TABLE 2). The diffusing capacity of the lungs was only moderately reduced Consequently, ventilation or diffusion did not limit the O_2 transport. The low arterial O_2 tension at rest might have been caused by uneven ventilation-perfusion relationships, and during exercise the alveolar-arterial O_2 tension difference decreased. Shunting of blood was slight or less than 5 per cent of the cardiac output as indi-

pulmonary artery pressure (100/43 mm Hg) and a high arteriovenous O_2 difference (81 ml./L) was found even at rest. The cardiac output was low (3 4 L per minute), and the stroke volume small (37 ml). Circulation thus represented the weak link in the chain of O_2 transporting mechanisms Angiography showed obstructions in the central branches of the pulmonary artery. The end-diastolic pressure of the right ventricle was elevated The small shunt indicated a closed foramen ovale This was confirmed at autopsy.

The low work capacity is primarily the result of the small stroke volume—37 ml Of a number of patients with mitral stenosis and a small resting stroke volume (see Chapter 13), none demonstrated a work capacity greater than 200 Kgm per minute (see FIG 6)

2 In case of a relatively small maximal cardiac output and thus a small circulatory reserve (as compared to the oxygen transport capacity of the other respiratory functions), arterial hypoxemia—resulting from either anatomic right-to-left shunts or venous admixture due to uneven ventilation-blood flow relationships—will limit oxygen transport (and work capacity) at a lower level than if the arterial blood had been saturated with oxygen. The arterial oxygen saturation is so low that the proportion of oxygen, which can be extracted by the tissues, is decreased. This will be manifested by a low arteriovenous oxygen difference along with the low arterial oxygen saturation (cf the similarity to the effect on maximal oxygen uptake of an enlarged physiologic dead space in cases with a small ventilatory reserve).

Extrathoracic Origin of Disturbed Ventilation

Disturbed regulation of ventilation may result in hypoventilation and arterial hypoxemia, whether or not they are caused by conventional ventilatory insufficiency of an obstructive or restrictive type, since the MVV may be far larger than that normally required for the maximal work performed. Such a condition is illustrated by a patient (Case 5) who seemed to have an impaired respiratory centrogenic drive resulting in hypoventilation, hypercapnia and arterial hypoxemia at rest and during exercise [23]

The patient did not increase ventilation when inhaling CO_2 mixture as do normal subjects or patients with emphysema and comparable hypercapnia (FIG 7) His work capacity at pulse 170 was lower than predicted from the heart volume, THb and blood volume, while the heart volume was normal in relation to the THb and blood volume He had normal lung volumes and a normal MVV which was much

value may be compared with that obtained in a quantitative evaluation of the O_2 transport capacity of some important respiratory functions, such as ventilation, diffusion and circulation, each of which may be limiting to the gas exchange and the physical work capacity.

The O_2 transport capacity of the different respiratory functions may be evaluated by lung function tests combined with examination of the circulation. The determination of the O_2 transport capacity of each of the important respiratory functions, together with a study of the O_2 concentration or partial pressure gradients across them, is a valuable method for determining which of the respiratory functions is the limiting factor for the O_2 uptake The function which has the smallest transport capacity also has the relatively largest O_2 partial pressure or concentration gradient across itself, particularly during exercise when function is stressed Conversely, the other respiratory mechanisms usually have a compensatory decrease in the O_2 gradient (FIG 8). This approach provides a useful method for determining whether circulation or the lung function limit the work capacity.

The patients chosen to exemplify the different conditions had severe functional impairment, which in most cases was evident at rest. In cases of moderate or slight pathologic disturbances, the functional significance of the pathologic changes appears only on exercise, and this may be quite difficult to establish without quantitative and objective methods.

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TABLE 3 —*Work Test with Measurement of Ventilation and Pa_{CO_2} in Case 6 (Respiratory Neurosis)*

Work load	At Rest	300	600	900 Kg /Min
Pulse after 6 min work	84	116	137	158 (after 1 min)
rf	30	57	~80	
V_E	9.4	26 0	41 6	
V_T	0 31	0 46	0 52	
Pa_{CO_2}	35	38	44	

An example of a patient of this type is Case 6 in TABLE 1, who after a traffic accident, which included a rib fracture, was quite incapacitated for several years because of shortness of breath He was examined on the request of an insurance company Roentgen examination of the lungs showed normal lung fields, free sinuses and a normal diaphragmatic mobility Several of the muscle groups in the back and shoulders were tense and contracted The results of the spirometric examination and the determination of MVV appears in TABLE 1 At an earlier examination elsewhere his VC was 1 5 L His behavior during the work test is described in TABLE 3 His peak work was only 600 Kg per minute, but extrapolated to pulse 170, his work capacity was estimated to be 1,000 Kgm per minute Lung compliance and resistance were in the normal range In connection with a work test, his dyspnea broke through the neurotic fixation of his respiratory muscles, and he was able to ventilate properly

CONCLUSIONS

Lung disease often limits the exercise tolerance considerably. This is often difficult to recognize clinically. By different more or less specific and objective lung function tests, it is possible to detect disturbed function in one or several respiratory mechanisms. By applying a work test, one can examine the different respiratory mechanisms when function is stressed and can analyze the significance of the various pathologic changes to the total function, i e., oxygen uptake and work capacity. In many cases, a work test alone is sufficient to rule out those pathologic changes in the lungs of significance to the total function.

Some normal relationships between the physical work capacity and some circulatory parameters, such as THb, blood volume and heart volume, are useful for predicting the magnitude of the possible gas exchange of a subject, if no pathologic changes were present. This predicted

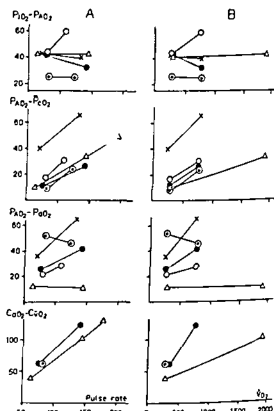


FIG 8 —Mean O_2 concentration or partial pressure gradients at rest and during exercise in relation to pulse rate beats/min (A) and O_2 uptake, $\dot{V}_{O_2}$ ml/min (B), from measurements in 12 normal subjects (△), 4 patients with emphysema (○), 5 patients with a low D_L ("alveolar-capillary block") (×), 3 patients with thrombo-embolism of the pulmonary artery (⊙), and 3 patients with severe mitral stenosis (●). Impaired ventilation (in emphysema) results in a large value for $P_{IO_2} - P_{AO_2}$, impaired diffusion in a large value for $P_{AO_2} - \bar{P}_{cO_2}$ (which is equal to $\dot{V}_{O_2}$/ 1 23 D_{LCO}), and impaired blood flow (in thromoembolism of the pulmonary artery and in mitral stenosis) in a comparatively large $Ca_{O_2} - C\bar{v}_{O_2}$, while the other O_2 gradients are usually compensatorily decreased, particularly in relation to pulse rate, which is used as an expression of the relative load on the circulation The $P_{AO_2} - Pa_{O_2}$ difference is included to show its magnitude and variability in different pathologic states The $Ca_{O_2} - C\bar{v}_{O_2}$ in normal subjects was not measured in the individuals from whom the O_2 partial pressure gradients were obtained[23] but in other subjects, i e 5 male controls[24] and 4 normal male subjects[25] The last mentioned group presented the highest $Ca_{O_2} - C\bar{v}_{O_2}$ difference (130 ml /L) at a mean pulse rate of 176 per minute and a mean $\dot{V}_{O_2}$ = 2,900 ml per minute However, the different groups showed quite similar relationships between work load, pulse rate, and O_2 uptake during exercise,[21 23,25] thus warranting the comparison

value may be compared with that obtained in a quantitative evaluation of the O_2 transport capacity of some important respiratory functions, such as ventilation, diffusion and circulation, each of which may be limiting to the gas exchange and the physical work capacity.

The O_2 transport capacity of the different respiratory functions may be evaluated by lung function tests combined with examination of the circulation The determination of the O_2 transport capacity of each of the important respiratory functions, together with a study of the O_2 concentration or partial pressure gradients across them, is a valuable method for determining which of the respiratory functions is the limiting factor for the O_2 uptake. The function which has the smallest transport capacity also has the relatively largest O_2 partial pressure or concentration gradient across itself, particularly during exercise when function is stressed Conversely, the other respiratory mechanisms usually have a compensatory decrease in the O_2 gradient (Fig 8) This approach provides a useful method for determining whether circulation or the lung function limit the work capacity

The patients chosen to exemplify the different conditions had severe functional impairment, which in most cases was evident at rest In cases of moderate or slight pathologic disturbances, the functional significance of the pathologic changes appears only on exercise, and this may be quite difficult to establish without quantitative and objective methods

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Section VII

RESTRICTIVE DISEASES OF THE CHEST

Paralytic Conditions

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THE power for ventilatory movements of the lungs is derived from the muscles of respiration These include not only those directly associated with the chest cage, but also the muscles of the abdominal wall, the shoulder girdle and the spinal column During quiet breathing, the diaphragm and intercostal muscles are principally active, but with more and more vigorous respiratory activity the ensemble is increased to include in one way or another most of the muscles of the trunk and upper extremities

FIGURE 1 schematically represents the muscles associated with the various pulmonary compartments and some of the factors which limit the magnitude of the vital capacity. The diaphragm is the most important muscle of inspiration, followed in importance by the spinal extensors, intercostals and accessory muscles of respiration. The most important muscles of expiration are the abdominal muscles, then the spinal flexors and intercostals It should be emphasized that the diaphragm is not a muscle of expiration, although by graded relaxation it can modify the expiratory flow pattern. The vital capacity is limited not only by the strength of the muscles involved but also by the degree of elasticity or compliance of the deformed structures On inspiration these are the lungs, rib cage and the abdominal wall, as well as the abdominal contents, on expiration the rib cage and diaphragm prevent complete collapse of the lungs, and thereby are responsible for the existence of the residual volume.

The normal respiratory muscles have great capabilities for power and endurance The significance of paralysis or impairment of respiratory muscles must therefore be assessed with a view to the respiratory demands of the patient and the degree of reduction of the normally large reserve capacity of respiratory muscles Although methods are available for measuring the capabilities of respiratory muscles, they are not well standardized and not widely enough used to be of much assistance to the physician who first suspects or encounters respiratory weakness, as in poliomyelitis

Respiratory Muscle Capabilities and Their Assessment

Common pulmonary function tests provide an indirect measure of muscle power and, in some tests, endurance as well Other factors also influence the results The vital capacity, for example, is a most useful test, but the value obtained is determined not only by muscle power but also by compliance of the lungs and thorax, air trapping, motivation, understanding of the test, practice and other factors. These are in addition to the effects of age, height and body position. The influence of many of these factors may be minimized by using the patient as his own control, i.e., by repeating the observation at intervals, when a change of respiratory muscle strength is suspected

The subdivisions of the lung capacity also are determined in part by the respiratory muscles, but again their effects are masked by other factors which contribute to the measurement Inspiratory capacity, for example, is influenced much by the initial relaxation volume (related to body position) and the compliance of the lungs as well as by the strength and mechanical advantage of the inspiratory muscles.

Maximum instantaneous flow rate and forced vital capacity measurements are affected by the variables mentioned above and, in addition, the air-flow resistance of the lungs and external airway. Although expiratory effort and power are reflected by these tests, there is no indication of endurance, since only three or four brief

efforts are required with rest periods between efforts.

The maximum breathing capacity (maximal voluntary ventilation), on the other hand, does *give some* indication of endurance. If the cooperation of the patient is good, the exercise during this test is severe, and exhaustion occurs within a short time even if respiratory alkalosis is *prevented*. Since flow rates are high, the resistive component of intrapleural pressure is high, and work rates are large for both inspiration and expiration. The serious disadvantage of *this test is that* its accuracy depends on maximal effort and cooperation, and these conditions are seldom obtainable in the acutely ill patient. Further, if a disease such as poliomyelitis is suspected, performance of the test with its attendant fatigue might promote the paralysis.

Other tests which measure respiratory muscle power *fairly specifically* have never come into general use These are methods which involve measurement of airway pressure under conditions of *maximum* inspiratory and expiratory effort and little or no air flow For example, the patient is asked to blow or suck maximally while his airway is connected to a manometer. In practice it is best to have a small leak in the system so that erroneous pressures cannot be obtained by closure of the glottis and use of the cheeks and tongue The maximum pressures depend on the amount of air in the lungs when the effort is made, inspiratory efforts develop largest negative values when the lungs are nearly empty, expiratory efforts are most effective when the lungs are well filled, as one would expect. Maximum pressures vary with physical fitness and training, normal values are approximately −100 mm. Hg on inspiration and +140 mm. Hg on expiration. These tests might prove valuable if they were standardized and used in conjunction with the vital capacity and maximum flow-rate measurements.

Types of Respiratory Paralysis

Breathing movements may be impaired or eliminated by several kinds of attack on the neuromuscular apparatus of breathing. Any injury, or drug, or other agent which interrupts the normal activity of the respiratory centers

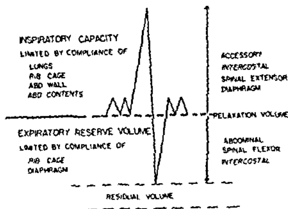


Fig 1—Muscular and mechanical factors which influence pulmonary compartments

will interfere with the ventilation of the lungs. Without considering the complex of neural and chemical factors which regulate the activities of the control mechanism, one may say that the medullary respiratory centers have an automatic rhythmicity, that the frequency and intensity of discharge can be inhibited by a large number of agents and facilitated by a lesser number, and that localized disease in the medulla may cause further disruption of function.

Thus, the virus of poliomyelitis, by its action on the medulla, may cause hypoventilation, arrhythmia and incoordination of respiratory muscles. Many narcotic and anesthetic drugs cause hypoventilation by inhibiting the reaction of the respiratory center to slight changes of CO_2 *tension and pH* A few drugs, *like the* salicylates, stimulate the center to cause hyperventilation and respiratory alkalosis.

Other agents, such as electric shock and head trauma, may also depress or paralyze the respiratory centers. Severe depression or paralysis requires immediate and continued artificial respiration until the center recovers normal function. In some instances, the respiratory muscle paralysis will only be part of a general paralysis. The precise nature of the respiratory paralysis is, however, an academic question, and one which *does not influence* therapy.

Respiratory muscles may be weakened or paralyzed by *peripheral* lesions in the spinal cord, in the *nerves themselves*, or in the myoneural *junction. For example*, in poliomyelitis *destruction of the anterior* horn cells produces

a flaccid paralysis of the peripheral muscle or muscles, infectious neuronitis also produces flaccid paralysis; and in myasthenia gravis there is failure at the myoneural junction.

Pathologic Physiology of Respiratory Muscle Impairment

In theory, respiratory paralysis could exist as a defect of the ventilatory pump, without associated disease in other parts of the respiratory system, in fact, this is seldom if ever the case. In the acute apnea of drowning, carbon monoxide poisoning, and other intoxications, the lungs are also involved, usually by pulmonary vascular engorgement and excess of alveolar fluid. The latter may be a true pulmonary edema caused by increased capillary filtration or leakage, or may represent the intrapulmonary accumulation of secretions aspirated from the pharynx or tracheobronchial tree Irrespective of source, the increased fluids cause mechanical alterations of the lungs which disturb the distribution of ventilation and increase the force required for adequate ventilation of the lungs.

Measurements of the distensibility or compliance of the lungs and thorax in patients paralyzed as a result of poliomyelitis have shown that these structures are two to three times as "stiff" as normal The increased stiffness or decreased compliance of the lungs occurs during the acute illness and appears to parallel the fall in the vital capacity Similar observations during the acute illness have not been satisfactory in evaluating the changes in the thorax During the convalescent phase, measurements of the functional residual capacity indicate that this volume is within normal limits when related to absolute values or to the patient's predicted total lung capacity. This implies that both the lungs and the thoracic structures must have changed equally and in such a way that the balance of forces has not been altered. This does not rule out the possibility of small areas of atelectasis associated with compensatory areas of overdistention, so that the volume has not changed. This could explain the altered compliance of the lungs

The atelectasis could be the result of forces of surface tension which are accentuated as parts of the lung approach their collapsed state A similar mechanism may also account for the altered compliance of the lungs that has been observed during anesthesia and during prolonged shallow breathing in a recumbent position. These losses of compliance due to local atelectasis can be prevented or reversed by occasional deep breaths. The increase in compliance brought about by occasional deep breaths means that less work should be required for breathing, and to the extent that more alveoli are patent there should be a better distribution of gas within the lungs.

One might anticipate that progressive respiratory paralysis would be manifested by evidence of inadequate ventilation—cyanosis, headache and other signs and symptoms as well as laboratory evidence of hypoxia and carbon dioxide retention. In fact, this is not the usual course of events, at least in respiratory poliomyelitis. The patient is usually recumbent due to the illness, so that metabolic needs do not call for utilization of more than a small fraction of the ventilatory capacity Therefore, a large part of the reserve may be lost, without anyone's awareness, unless the vital capacity happens to be measured at frequent intervals during the progression of the disease. As the reserve is lost, respiratory needs continue to be met by increasing effort of the muscles which are spared or which are least paralyzed. Hypoxia and respiratory acidosis may thereby be prevented until two-thirds or more of the ventilatory reserve is lost. Some authors have advocated the early use of respiratory aids and feel that when the vital capacity reaches one-half of the predicted value the patient should be given a trial, preferably in a tank respirator Respiratory assistance given at this time is not a life-saving procedure, the purpose of its use may be explained to the patient, and, most importantly, he may be promised to be taken out of the respirator after the trial. The latter possibility has much significance later during the "weaning" period. When the vital capacity reaches one-third of the predicted value it is desirable that the patient be in the tank more or less continuously. Some authors have set this lower limit at one-quarter of the predicted vital capacity.

Table 1 presents a simple technic whereby the vital capacity can be predicted. It must be emphasized that this is not as accurate as other methods in the literature, but it does have clinical usefulness, is easy to remember and is easy to calculate at the bedside

If the patient is sufficiently ill, febrile and apprehensive, he is likely to overventilate rather than to underventilate his lungs. This excessive breathing activity is a manifestation of the emotional response to the disease and appears to be the cause of several problems. The extra demands on already weakened muscles constitute a stress which may lead to further impairment If the overventilation is continued, it leads to progressive adaptation to the new levels of CO_2 tension and pH, and thus tends to perpetuate itself. When artificial respiration is given, it also must meet the heightened demand for ventilation, and dependence on the machine is increased

Physiologic Aspects of Treatment of Respiratory Paralysis

If apnea exists, the need for immediate artificial respiration is clear, and the external source of energy must be continuously available until natural breathing becomes adequate[5] Several methods and devices have been developed to supply or assist pulmonary ventilation in the operating room, at the scene of accidents, in wards devoted to respiratory poliomyelitis treatment, and in many other situations It is not within the scope of this chapter to deal with anything beyond the general principles of these methods and the physiologic principles to which they are related.

Acute Apnea

The problems of acute apnea are the need for speed, the complicating factors which limit the effectiveness of ventilation, and the degree of circulatory impairment. The first point does not need emphasis to physicians, who realize the scarcity of oxygen stores in the body and the susceptibility of the heart and brain to severe hypoxia of only a few moments' duration

The complicating factors which limit the effectiveness of artificial respiration procedures

Table 1 —*Clinical Prediction of Vital Capacity*

	Children 5-15 yr	Adults 16 yr and over
Males	250 cc /yr age	25 cc /cm. ht
Females	200 cc /yr age	20 cc /cm. ht

do deserve emphasis. Most obvious is the requirement of a clear airway; this is usually obtained by having the patient in a prone position, if possible, and by keeping the jaw pulled forward. The prone position facilitates drainage of fluids by gravity from most of the tracheobronchial tree and from the pharynx. In some instances, the fluids may be too viscous and tenacious to flow freely. If drainage by gravity is impossible or inadequate, more radical measures must be used, such as intubation or tracheotomy When such procedures are done, a tube which approximates the internal diameter of the trachea must be used to minimize resistance In addition, the inspired air should be saturated with water vapor at body temperature to prevent drying and encrusting of secretions in the tracheobronchial tree, since a tracheostomy bypasses the nasal and pharyngeal mucosa where warming and humidification of inspired air normally take place

Figure 2 shows the relationship of the vapor tension of water to temperature. On the right is the capacity of the air in grams per liter. Note that when air is 50 per cent saturated at room temperature (24C) it contains about 0.01 Gm./L When this air is warmed and saturated at body temperature (37C) it contains about 0.045 Gm./L, approximately 4½ times as much water. If fever is present, the capacity will increase even more. If moisture is not added prior to inhalation, then moisture must be added by the respiratory system Thus, when air with a low water content is inhaled through a tracheostomy tube, extreme drying of the tracheal secretions may result

As mentioned earlier, the lungs of the acutely apneic patient may be much less compliant than normal, due to aspirated secretions, pulmonary edema and possibly other factors. As a consequence, manual methods of artificial respiration may be ineffective and even mechanical aids or mouth-to-mouth breathing may not be adequate unless the force brought

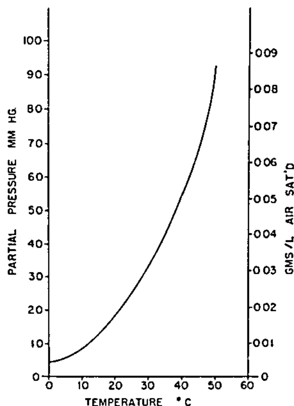


Fig 2.—Effect of temperature on vapor tension of water

to bear on the lungs can be sufficiently increased The implication is that the effectiveness of a method cannot be predicted when applied to a given patient, since the ventilation developed by the method is dependent not only on the force and timing of the method but also on the mechanical characteristics of the lungs and thorax of the patient himself. The proper solution of the problem is to measure, when possible, the levels of O_2 and CO_2 in the arterial blood, and, failing this, to measure the minute volume of ventilation and breathing frequency during use of the method.

The circulatory state of the apneic patient is frequently unknown. In some cases, the apnea may be associated with a high central venous pressure and a high tolerance to positive pressure breathing, as in cyclopropane anesthesia. More often, the apnea is associated with low cardiac output, low vasomotor reactivity and increased susceptibility to the circulatory effect of positive pressure breathing. The mechanisms of these possible effects have been well established and are well known. The differences of opinion which may be found in the literature are mostly a question of the practical importance of such mechanisms.

When apnea is treated by electric stimulation of a phrenic nerve, the beneficial effects of natural breathing are seen in the rise of arterial blood pressure and in the increase of cardiac output. Similar effects could be expected of any method which causes inspiration by the lowering of intrathoracic pressure. This effect has been claimed for the tilting method of artificial respiration, but no quantitative study of circulatory changes has yet been made.

Most methods of artificial respiration cause inspiration by increasing intrapulmonary (and to a lesser extent intrapleural) pressure relative to the pressure which pertains to the rest of the body (normally atmospheric, but in a body-enclosing respirator—the intratank pressure). As a result of the loss of negativity of intrapleural pressure, the normal inspiratory enhancement of venous return is replaced by a temporary reduction of venous return. This inspiratory impairment of blood flow may be made up during expiration, dependent on the timing and pattern of applied pressure and on the ability of the circulation to respond to positive pressure breathing. The compensatory mechanisms are principally the capacity for vasoconstriction, an adequate blood volume, good myocardial contractility and good abdominal muscle tone These mechanisms, when normal, are able to maintain cardiac output and blood pressure in the presence of a high intrapulmonary pressure, but in the presence of apnea some of the mechanisms are likely to be deficient. For this reason it is urgent that the mean positive mask pressure (or the mean difference between pressure in the lungs and pressure around the body) be kept as low as possible. The anesthesiologist aims to achieve this objective by brief sharp pressure on the anesthesia bag for inspiration, with an expiratory phase at least as long as inspiration. The manufacturers of one class of the devices known as "resuscitators" aim to maintain a low mask pressure by incorporating a suction mechanism which lowers the mask pressure below atmospheric during the late part of expiration. In a patient who responds poorly to positive pressure breathing, these devices produce less im-

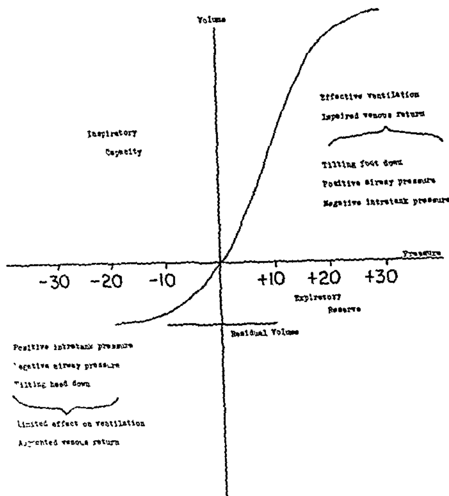


FIG 3.—Effect of applied pressure or tilting on ventilation and circulation

pairment of circulation than do the all-positive respirators, but their effects in general are more like those of positive pressure breathing than those of natural breathing A listing of circulatory effects of several methods is given in FIGURE 3.

In summary, acute apnea requires immediate restoration of oxygen supply by a method which ensures a clear airway and is capable of developing enough force to deliver O_2 to lungs which are usually uncompliant and often partially blocked internally. The method should promote circulation also, if possible, or at least interfere with blood flow as little as possible. Because of the large capacity of the body to absorb CO_2, precise control of ventilation is not essential in the early minutes of artificial respiration.

CHRONIC APNEA

Problems of this type occur most commonly in respiratory poliomyelitis, although in essential details the picture is the same if respiratory paralysis is due to multiple sclerosis, myasthenia gravis, brain trauma, long-acting drugs or neuromuscular disorders. In this type of patient, the control of ventilation is quite important, and the circulatory effects of artificial respiration are seldom of consequence. Mechanical alterations of lungs and thorax are just as prominent as in acute apnea, although the pathologic process may not be the same.

The ventilation requirement of patients with prolonged respiratory paralysis or weakness are affected greatly by the extent of paralysis of nonrespiratory muscles and the degree of general bodily wasting The adjustment of ventila-

tion to rate of CO_2 production is in part the responsibility of the physician, even though the competence of the respiratory center may have been initially unimpaired. Hyperventilation may occur because of anxiety, fever, proprioceptive reflexes from pressure breathing machines and other factors. Once established, the hyperventilation tends to continue indefinitely, at least if one of the exciting factors remains in operation. Hypoventilation may also develop if respiratory muscles become overfatigued or if the respiratory center is temporarily depressed by sedative drugs or an anoxic episode If hypoventilation continues until acclimatization takes place, the return to a normal ventilation rate must be accomplished gradually.

Because of the refractory nature of chronic hypoventilation or hyperventilation, it is extremely important to keep the ventilation at a normal level continuously from the beginning. This goal can usually be achieved with the aid of measurements of arterial pH and CO_2 or alveolar CO_2, if these methods are not available, satisfactory control may be obtained by use of tidal volume measurements and a nomogram which relates body weight and respiratory frequency to the tidal volume necessary for a normal CO_2 tension in the arterial blood[11] A low resistance ventilation meter is essential for successful use of this method Corrections should be made for fever, activity and the presence of a tracheostomy.

If ventilation is maintained at a level suitable for carbon dioxide homeostasis, the oxygen supply will usually be taken care of simultaneously. However, in the presence of pulmonary edema and infection, local areas of hypoventilation may be sufficient to cause hypoxia, although carbon dioxide elimination is unimpaired. When this occurs, oxygen enrichment of inspired air is needed rather than increased ventilation.

Dependence on tank respirators or other fully effective forms of artificial respiration should be discouraged by removing the device as early as possible during convalescence This is done by means of a program of gradually increasing reliance on natural breathing. Very short periods in the beginning are lengthened as the patient can tolerate unassisted breathing without fatigue or undue anxiety. Partial assistance may be given, usually by a form of cuirass respirator.[1]

Typically, a convalescent patient, with even severe respiratory involvement, may within a few weeks spend only the night in a tank respirator and the rest of the time in a cuirass or on a rapidly rocking bed. Cuirasses play a valuable role in convalescence but are not very effective in ventilating the lungs, unless they cover the whole abdomen; even so, they are only about two-thirds as effective as methods which apply a pressure difference to the whole body. The rapidly rocking bed produces ventilation by cyclic tilting of the body at a rate which approximates normal breathing frequency. The principal mechanism of this action is the change of relaxation volume of the lungs brought about by gravitational forces acting indirectly on the diaphragm.[2] Tilting in the foot-down direction causes an inspiration associated with an increased negativity of the intrapleural pressure. Tilting in the head-down direction is less effective than the foot-down position since the diaphragm quickly acts as a stop. The gravitational forces are related to the mass of the abdominal contents and to the length of the abdomen. Rocking through a comfortable angle of motion will usually cause sufficient ventilation, unless the abdomen has too little mass, or is too short, or unless downward movement of the diaphragm is impaired by increased intra-abdominal pressure. Adults and children require approximately the same change of intrapleural pressure to produce an adequate tidal volume. Children are therefore less effectively ventilated on a rapidly rocking bed, since a short abdomen with low mass may be insufficient to produce an adequate hydrostatic pressure head.

During convalescence, repeated measurements of the vital capacity may be used as a guide to determine the length of unassisted time a patient can tolerate When the vital capacity is about 10 per cent of predicted, the patient can usually breathe 15 minutes to half an hour continuously unassisted. As the vital capacity increases, longer periods of unassisted breathing may be expected. When it is about

one-third of predicted, patients usually do not need any breathing aids. There is some variability from patient to patient, depending on which muscles are producing the vital capacity and are used for the unassisted breathing. If breathing is the result largely of diaphragmatic action, the unassisted time will be longer than if breathing is the result solely of the accessory muscles of respiration.

Such criteria do not apply to those patients with severe respiratory muscle paralysis who are able to do glossopharyngeal breathing[3]. By this technic, sequential volumes of 100 to 150 cc. are forced into the lungs by the tongue and pharyngeal muscles. The glottis is closed at the end of each stroke. When a sufficient volume has been forced into the lungs, expiration takes place passively due to the elastic recoil of the lungs and thorax. Some patients who have developed this ability can breathe for as long as 16 to 18 hours continuously unassisted.

This technic may also be used to stretch the lungs and thorax and to assist persons to "cough." If patients are unable to stretch their lungs and thorax by this technic, stretching can be done by temporarily increasing the negative tank pressure by means of a booster or blower. Such a procedure may also be done by means of positive pressure at the mouth. There is some evidence that such stretching increases distensibility, and may have other beneficial effects on the lungs. The distending maneuver or occasional deep breath may also be used during the acute illness to help prevent atelectasis.

Whenever artificial respiration is necessary for as long as several days, other systems of the body may be secondarily involved. Such complications include gastrointestinal dilatation and, secondary to the prolonged immobilization, negative calcium and nitrogen balances. Urinary retention with resultant catheterization and urinary tract infection may in combination with the increased urinary calcium excretion result in nephrocalcinosis. There is also a likelihood of thrombophlebitis of a leg vein.

This section was written with the intent of emphasizing the physiologic features of paralytic conditions and their treatment. The references which follow are suggested for more detailed consideration of clinical problems and methods of therapy.

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Thoracic Deformity and Cardiopulmonary Disease

Kyphoscoliosis, Rheumatoid Spondylitis, Pectus Excavatum, Fibrothorax

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CARDIOPULMONARY function may be adversely influenced by displacement or disease of the thoracic cage. Local or generalized disease can involve one or more of the tissue layers of the chest including the pleura, but deformity and disease of the bones and cartilaginous joints of the thorax or the delicate pleural membranes may be especially harmful. It is not always certain that physiologic defects are strictly the result of the mechanical disadvantage to which the lungs and heart are subjected or whether pathological changes in the cardiopulmonary system also contribute to the measurable abnormalities.

A significant skeletal deformity with normal tissues may produce marked asymmetry of the thorax and severe distortion of the intrathoracic contents. As, for example, in severe kyphoscoliosis, there is a measurable alteration of physiologic functions, whereas in pectus excavatum asymmetry is rare; displacement of the heart is unusual, and physiologic abnormalities are uncommon. The defect in rheumatoid spondylitis is due to immobility, the diaphragm is not specifically involved and functional loss is mild

Disease of the tissues of the chest wall may produce severe functional derangements, despite apparent structural integrity and normal symmetry. Indeed, a rigid pleura is more serious than a rigid skeleton. In fibrothorax the immobility of the rib cage is usually limited to one hemithorax but functional loss is often severe; the diaphragm may be affected secondarily. Abnormalities of the skin capable of influencing functional capacity are rarely noted In one case of scleroderma, there was a restrictive type of ventilatory insufficiency, due solely to skin changes with no apparent underlying pulmonary disease Cicatrical contractures following extensive burns may produce mild similar changes

Trauma to the chest wall, either accidental or surgical, will naturally exert a profound effect on cardiopulmonary function. Pulmonary resection and collapse procedures, especially the older types of thoracoplasty, may resemble spontaneous kyphoscoliosis as follows: (1) cardiopulmonary failure developing many years after the deformity becomes established, (2) right heart hypertrophy and the clinical features of cor pulmonale and (3) poor correlation between the severity of the deformity, the degree of impairment of cardiopulmonary function and the intensity of the patient's symptoms.

Kyphoscoliosis, rheumatoid spondylitis, pectus excavatum and fibrothorax—the four conditions to be discussed—may have no effect on physiologic function, or they may produce physiologic derangements which differ in severity but are similar in type. These changes include reduced lung volumes, diminished ventilatory capacity and increased work of breathing Cardiac complications and blood gas abnormalities develop irregularly whenever lung function is markedly reduced.

Kyphoscoliosis

The existence of kyphoscoliosis as a clinical entity and its association with cardiopulmonary disease have been known since the time of

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Hippocrates It is interesting that Hippocrates believed thoracic deformity did not always produce disease, "....many have borne the affection well, and have enjoyed good health until old age...."[1] In the eighteenth and nineteenth centuries the medical literature on kyphoscoliosis dealt primarily with the patho- [illegible] deformities and [illegible] se [illegible] 40 years. It has been recognized, in recent years, that severe kyphoscoliosis does not necessarily produce cardiopulmonary disturbances at an early age, *and marked curvatures may be consistent with an almost normal life span*[8, 14, 24]

The first attempts to characterize the physiologic abnormalities in kyphoscoliosis probably date back to 1854 when Schneevought measured the diminished vital capacity with a spirometer.[25] Physiologic data were limited until 1939 when Chapman, Dill and Graybiel[6] published their detailed review of 12 cases including 8 studied by modern physiologic methods.[6] In 1958, Hanley et al. published physiologic data on 24 patients emphasizing the disturbances in those patients who developed heart failure [14]

The deformity known as kyphoscoliosis represents a combination of an excessive or abnormal anteroposterior curvature, a lateral curvature and an associated rotation of the spine and trunk (Fig 1). Kyphosis or scoliosis may exist independently. The former is the more striking single deformity with respect to the onset of cardiopulmonary dysfunction. When an abnormal curvature exists in one region of the vertebral column, a lesser, compensatory curve develops *elsewhere.*

The type and extent of the skeletal deformity can only be assessed by appropriate radiologic study (Fig. 2). The literature contains detailed descriptions of methods for measuring the angle of the primary curve and the associated rotation[19], however, such precise technics have been utilized only in growing children as an index of whether their deformity is progressive or stationary. Inasmuch as there is no satisfactory method for grading the severity of the thoracic deformity, Hanley used facsimiles of the postero-anterior and lateral chest x-rays to illustrate the extent of the spinal curvature [14] The interpretation of thoracic roentgenograms with regard to pulmonary or cardiac pathology may be extremely difficult due to the marked *distortion of the thoracic contents This distortion* often results in one hemithorax being considerably larger in its anteroposterior diameter than the other. The determination of specific cardiac chamber enlargement is frequently impossible.

There are two important types of kyphoscoliosis in children: the type that is secondary to poliomyelitis, and idiopathic scoliosis. The idiopathic type is the most common, and three-quarters or more belong in this category.[3] During childhood, there is a greater frequency



Fig. 1 —*Patient D J* Idiopathic kyphoscoliosis Age 10 and 30 years Spinal fusion at age 11. Patient is an active housewife, mother of two, *no complaints*

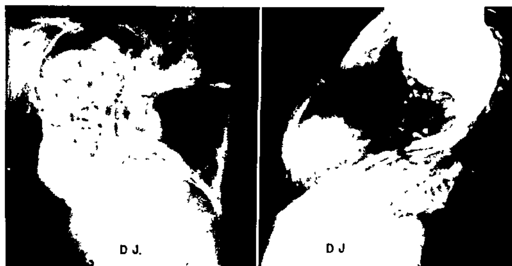


FIG 2 —Patient D J , age 30 years, PA and lateral chest roentgenograms Vital capacity, 875 ml , maximal breathing capacity, 34 L per minute Forced expiratory capacity, 1 sec , per cent of total vital capacity, 85 per cent Resid vol /total lung cap ratio, 41 per cent (Case referred by Chicago unit, Shriners Crippled Childrens Hospital)

among girls, a four to one female to male ratio The etiology of the deformities noted in middle-aged or older adults can only be surmised Data are not available on the sex ratio in adults, but a preliminary survey indicates that it differs considerably from the ratio in children. From 1953 to 1958, a diagnosis of kyphoscoliosis was made in 61 instances in a group of 6,473 patients admitted to a large geriatric hospital, the incidence of kyphoscoliosis was 0 85 per cent for males and 1 11 per cent for females[7] The marked difference in sex incidence in children as opposed to adults is not generally known An equally baffling aspect of kyphoscoliosis in both children and adults is the preponderance of a primary right thoracic curve.[1, 6] This malformation causes a decrease in the size of the left hemithorax, and with a severe curvature the heart and left lung are "caught" between the iliac crest and the left lateral rib cage. This has been suggested as a possible reason for the occurrence of cardiopulmonary failure in severe *kyphoscoliosis*.[6]

There is a striking reduction in the vital capacity of patients with kyphoscoliosis. In 1928, Flagsted studied 100 patients with kyphoscoliosis in an attempt to correlate the location of the deformity, its severity and the associated muscle weakness with the vital capacity.[12] He concluded that severe curvatures of the cervical or thoracic spine caused a reduction of vital capacity, but with involvement o the lower thoracic or lumbar regions the vita capacity was not affected Muscle weaknes resulted in a relatively insignificant loss of vita capacity—beyond that produced by the primary skeletal deformity.[12] Marked reduction in total vital capacity are reported in the obstetric literature In 11 women with sever kyphoscoliosis the vital capacity range was 60 to 1,400 ml. throughout pregnancy and afte delivery.[16 20 25] There was no correlation between disability, symptoms and vital capacity

All lung volumes are small in the majority o patients with kyphoscoliosis The residual volume and the functional residual volume compartments were reduced in all but 4 of 40 case reviewed [6, 14, 15, 13] The reduction of vital capacity is greater than for the other volume compartments; therefore, the residual volume occupies a greater than normal percentage of th total lung volume.

Intrapulmonary gas distribution is remarkably uniform, whether measured by a helium dilution[15] or nitrogen elimination method.[8, 14] These findings are at variance with the concept that the compressed lung, which is poorly ventilated, acts as a localized source of physiologic difficulty.[14] With partial bronchial occlusion and poor ventilation, normal intrapulmonary gas-mixing pattern would not be expected. It should be mentioned that in certain kyphos-

coliotic patients with homogenous intrapulmonary gas distribution and a smaller than normal functional residual volume, nitrogen elimination is more rapid than in normal subjects.

Ventilation alterations are consistent with patients exhibiting markedly reduced but otherwise normally functioning pulmonary parenchyma. Indeed, recorded maximal breathing capacities vary from normal to very low values.[14] By and large there is a concomitant reduction of maximal breathing capacity and vital capacity, but with a relatively greater loss of vital capacity.[8,14] Consequently, the ratio of maximal breathing capacity to vital capacity (both expressed as a per cent of their predicted value) is greater than one. This ratio is known as the air velocity index,[13] and signifies restrictive ventilatory insufficiency when it exceeds unity. A value of less than one is observed whenever obstruction to airflow (obstructive ventilatory insufficiency) predominates.[13] Airflow obstruction is not a part of the physiologic abnormalities of severe kyphoscoliosis. This is further apparent in the timed expiratory capacity tests. A normal proportion of the small total vital capacity is expired promptly.[15]

The minute ventilation in kyphoscoliotic patients is occasionally higher than normal[6,15] but measurements made at rest in the laboratory probably bear little relation to what happens in more familiar surroundings; the respiratory rate is frequently increased and there is the appearance of breathing excessively. The significant fraction of the total ventilation—that portion which reaches the alveoli and participates in metabolic exchange (alveolar ventilation)—may be smaller than normal. A low alveolar ventilation is likely to occur whenever the respiratory rate is rapid and the tidal volume is low. Such a combination produces a large total ventilation, but it is the respiratory dead space which is ventilated and not the physiologically more important alveoli. Abnormally low alveolar ventilation has been predicated as the reason for cardiopulmonary failure, cor pulmonale and death in kyphoscoliosis by Fishman, Turino and Bergofsky.[16]

It is apparent that the ventilatory and lung volume abnormalities in kyphoscoliosis are those of restrictive ventilatory insufficiency—reduction of all lung volume compartments, normal intrapulmonary gas distribution and no evidence of airflow obstruction. These are opposite to the findings in emphysema in which the residual volume is substantially increased and airflow obstruction readily demonstrable with unevenness of gas distribution. Emphysema occurs in kyphoscoliotic patients, but the distinct differences in ventilatory function and lung volume changes between uncomplicated cases of kyphoscoliosis and the more commonplace emphysema should provide satisfactory criteria for differentiation. Snider found physiologic abnormalities consistent with emphysema in 15 of 27 kyphoscoliotic patients.[24]

The work of breathing in kyphoscoliotics is increased.[5,11] The act of breathing requires energy expenditure to overcome: (1) the resistance of the chest wall and lung parenchyma to deformation and (2) the resistance of airflow through the tracheobronchial tree. Airflow resistance is normal, as indirect measurements with the previously mentioned dynamic ventilatory function tests have shown. Deformation of the lungs and chest wall, essentially elastic structures, requires an abnormally large energy expenditure. This increased elastic resistance—also known as decreased compliance—is the major abnormality in the mechanics of breathing of these patients. Normal subjects as well as patients with cardiorespiratory disease select the breathing pattern which requires minimal energy expenditure[2]; usually very little energy is needed to deform the chest wall and lung parenchyma to accommodate a tidal volume of 1 to 2 L. In kyphoscoliotic patients, excessive work is required for small increments in the tidal volume. Consequently, these patients attempt to improve ventilation through acceleration of the respiratory rate rather than increasing the tidal volume. This may not provide adequate alveolar ventilation to maintain normal blood values.

Arterial oxygen unsaturation is generally marked only in patients with overt or compensated heart failure[15], and carbon dioxide retention is roughly proportional to the degree of hypoxemia. In 3 patients studied during heart failure and after recovery, the arterial oxygen and carbon dioxide improved but were

not restored to normal.[18] It has been found also that in the absence of any cardiac complications arterial blood gas values are usually normal.[6]

When arterial oxygen unsaturation and carbon dioxide retention exist, sedative drugs and oxygen administered in high concentrations, separately or in combination, may be fatal Under these circumstances, there is reduced sensitivity of the respiratory center to carbon dioxide as a breathing stimulus, and with lowering of pH, narcosis may supervene and the patient may succumb due to respiratory acidosis. Failure to recognize this unfortunate sequence of events probably explains the repeated observation that hunchbacks are peculiarly sensitive to morphine sulfate [6, 9, 17] In a study of 6 severely deformed but clinically well patients, there was no significant change in arterial oxygen and carbon dioxide tension following the administration of 10 to 15 mg of morphine sulfate [8] Thus, the previously emphasized hazard of morphine administration in kyphoscoliosis should be reconsidered in light of the known adverse physiologic response to a respiratory depressant which any patient with carbon dioxide retention may exhibit. (Morphine may reduce the cough reflex, a disturbing action in bronchial infections.)

A systematic evaluation of cardiac function in kyphoscoliotic patients by means of venous catheterization is somewhat limited Schaub has reasonably complete data on 6 patients[22] and Bergofsky et al. have studied 13 [2a] Schaub attributes the cardiac complications to a reflex constriction of the pulmonary arterioles secondary to hypoxia This initiates hypertension in the lesser circuit, which later becomes fixed Bergofsky believes that alveolar hyperventilation occurs first, the result of a compensatory breathing pattern secondary to the thoracic deformity Arterial blood gas abnormalities are the inevitable consequence of alveolar hypoventilation. Hypoxemia was not necessarily a precursor of pulmonary arterial hypertension but when present the hypertension was more severe. He postulates that the elevated pulmonary pressure is secondary to an abnormal resistance to the flow of blood through the pulmonary vascular bed. The factors responsible for this increased resistance appear to be (1) mechanical compression of the vascular bed (2) anatomic thickening of the precapillary vessel wall; and (3) effects of hypoxemia.[2a]

Rheumatoid Spondylitis

Rheumatoid spondylitis was first reported by Bernard Connor in 1691.[29] Sydenham described the clinical features of ankylosing spondylitis and distinguished the condition from other forms of rheumatism during the latter portion of the seventeenth century.[33]

Rheumatoid spondylitis is believed by some to represent a vertebral variety of rheumatoid arthritis.[37] The sacroiliac and spinal joint changes that cause low back pain, morning stiffness and limitation of spinal motion, and the characteristic radiologic changes are usually adequate to differentiate ankylosing spondylitis from the other types of arthritis Nevertheless, it should be mentioned that peripheral joint involvement occurs in 25 to 30 per cent of patients with ankylosing spondylitis [32, 40, 41] The condition is inherited as a simple autosomal dominant with slightly reduced penetrance [31] Males are primarily affected in a ratio of 10 to 1, although in the familial form this ratio is less exaggerated.[31, 40, 43] The morbidity is highest in the 15 to 35 year age group [26] The disease is ordinarily self limited at any stage; but some cases are mild and gradually progressive, others severe and rapidly progressive. The typical features are limited spinal motion, loss of lumbar lordosis, fixation of the thorax with forward projection of the head and rounded stoop of the thoracic spine. About 63 per cent of the patients develop kyphosis, although this is neither severe nor associated with rotation or scoliosis [29]

The paucity of pulmonary symptoms in patients with rheumatoid spondylitis is striking, as illustrated in a group of 311 cases reported by Blumberg with no striking disability related to pulmonary manifestations [26] The loss of chest expansion resulting from immobile costovertebral and sternomanubrial joints has been considered pathognomonic of the disease. In this connection, a doubly exposed chest roentgenogram at full expiration and inspiration will demonstrate the range of diaphrag-

matic motion and complete absence of rib motion.[33,34] Indeed, more than 50 per cent of the patients have a chest expansion of less than 1 inch during full inspiration.[25,34] There apparently is a direct relationship between the limitation of chest expansion and the vital capacity, since the volume is consistently reduced to 50 to 75 per cent of the predicted value.[29,30,34,42] It should be mentioned, however, that a similar reduction of the vital capacity occurs in normal subjects when the chest is restricted by taping or by a laced jacket.[27,29] Forestier suggests there is augmentation of diaphragmatic motion in patients with rheumatoid spondylitis because of the relatively normal vital capacity in the presence of marked fixation of the rib cage.[29] In experiments on normal subjects with tight chest binders, augmentation or inhibition of diaphragmatic motion could not be demonstrated[27,29]

Residual lung volumes are normal The total lung volume is slightly reduced in proportion to the decrease in vital capacity. Therefore, the ratio of the residual volume to the total lung volume is increased[39]

The maximal breathing capacity is significantly reduced but not to the extent observed in severe kyphoscoliosis, and the reduction is proportionately less than the decrease in vital capacity. Consequently, the air velocity index exceeds unity. Normal timed expiratory capacities are additional evidence for a normal expiratory airflow velocity[28,39]

Arterial oxygen unsaturation below 95 per cent was reported by Julian in 6 of 14 patients. Eight of these patients displayed complications such as bronchitis, heart disease and emphysema In 3, the arterial P_{CO_2} exceeded 44 mm Hg[36]

The work of breathing is greater than normal in rheumatoid spondylitis patients because of the increased rigidity of the thoracic cage.[11] This is comparable to the situation in kyphoscoliosis in which the rigidity may result in alveolar hypoventilation It is unlikely that in rheumatoid spondylitis significant alveolar hypoventilation occurs with the production of hypoxemia of a degree sufficient to cause circulatory changes; cases of cor pulmonale have not been reported.

Robinson reported that 4.3 per cent of 352 patients with rheumatoid spondylitis showed clinical evidence of cardiac disease.[40] There is increasing evidence that a form of aortitis with aortic insufficiency is peculiar to rheumatoid spondylitis,[26] although other valvular lesions have been reported

Pectus Excavatum

In 1594, Bauhinus first described pectus excavatum and its clinical manifestations.[45] Ebstein, in 1882, collected 5 cases and gave them the name "trichterburst." More recently Ochsner and De Bakey[46] reviewed the literature and described the features of a case. Since, a number of cases has been reported[45,46]

Pectus excavatum or funnel chest is a congenital thoracic malformation consisting of a depression of the lower portion of the sternum and the adjacent costal cartilages. The depth of the sternal depression is usually maximal at the xiphoid with a symmetrical inward bending of the costal cartilages This deformity is noted at birth or soon thereafter, it is frequently familial).[57] The condition is not rare, the incidence being about 0 6 per cent.[52] Males predominate in a ratio of about 4 to 1[53]

The cause of pectus excavatum is obscure. The defect is progressive, involving primarily the anterior chest wall during the years of growth Theories as to cause are as follows (1) an abnormally developed anterior portion of the diaphragm pulling on the xiphoid attachments[60], (2) neuromuscular imbalance or overstimulation of the anterior diaphragmatic fibers[34], (3) shortening of the central tendon of the diaphragm[44,58], (4) disproportionate growth of the lower ribs.[49,40] A combination of the latter two theories is generally accepted, although very little proof of these mechanisms exists This deformity is seen with Marfan's syndrome and is frequently associated with other congenital defects.

An index of the severity of pectus excavatum is the distance between the xiphoid and the vertebra and is best measured by obstetric calipers or lateral x-ray pictures with a layer of barium in the sternal depression[43,52] (Fig. 3). The heart may be displaced into the left hemithorax, rarely to the right, or posteriorly be-



FIG 3 —Lateral chest roentgenogram, pectus excavatum, illustrating posterior displacement of the xiphoid (Reproduced by permission of W B Saunders Co, from Koop, C S Clin North America 36 1627, 1956)

tween the sternum and the spine.[44] The sternal depression may be maximal in infancy, decreased in childhood and becomes stationary; or it may increase gradually until adulthood After full growth, further progression is rare unless associated with other thoracic deformities such as kyphosis or scoliosis

Most cases have few or no symptoms When present, the symptoms may not reflect the severity of the sternal depression Psychologic problems associated with the pectus malformation, particularly in young males, are the most prominent features.[45] With actual displacement, distortion or compression of the thoracic viscera, functional symptomatology may occur [49]

The depressed sternum will compress or limit expansion of the lung. Occasionally, the diaphragm is distorted and its range of motion decreased, resulting in diminished pulmonary ventilation, and reduced vital capacity.[49, 59] The reduction in vital capacity and maximal breathing capacity has not been fully correlated with the extent of the sternal depression A significant reduction of the maximal breathing capacity is occasionally noted.[59] Of interest are reports of an increase in the maximal breathing capacity following corrective surgery.[44 52]

The cardiac symptoms and signs are more difficult to evaluate than the pulmonary manifestations Soft systolic murmurs, Grade 1 to 3 in intensity, and nonradiating, are frequent and may disappear after corrective surgery Atrial tachycardia and fibrillation have been reported [45 46] The electrocardiograms are generally not significant [49 54 59] In 22 cases, Fabricus reported 10 with normal electrocardiograms, 8 with right axis deviation, 2 with right bundle-branch block, 1 with left axis deviation and 6 with abnormal P waves.[47]

In a study of 22 patients with cardiac catheterization, only a few minor abnormalities were noted [47] Several observers have described a right ventricular pressure curve resembling that observed in constrictive pericarditis—a diastolic dip and an elevated end diastolic plateau—suggesting compression of the right ventricular chamber [47 53] With significant distortion and or compression of the heart by the depressed sternum, cardiac symptoms have developed.[46 52 54] Cardiac failure in young adults has been relieved by corrective surgery In the case of a 28 year old male treated surgically, there was a gradual return to normal of the right atrial and ventricular pressures, and the cardiac output increased [57]

FIBROTHORAX

Approximately 20 years ago thoracic surgeons found that peeling of the thickened pleural membrane from an encased lung due to fibrothorax restored pulmonary function Duration of the disease and the degree of parenchymal involvement were factors in the degree of recovery The results have stimulated an interest in the pathophysiology of fibrothorax.

The normal pleura is paper thin, transparent, flexible and elastic. As thickening occurs, the pleural surfaces fuse and contract. In progressive cases, the intercostal spaces are narrowed,

the involved hemithorax reduced in size and the mediastinum is displaced to the affected side. With pleural fibrosis, pulmonary ventilation becomes increasingly impaired due to this restriction. Constrictive calcific bilateral fibrosis may result in complete loss of thoracic motion and even restriction of the diaphragm.[62]

A striking correlation has been noted between functional impairment and the volume of the lung bound down by the abnormal pleural membrane. The vital capacity may be 50 to 65 per cent of the predicted volume.[65, 67] In one case of bilateral fibrothorax the value was only 900 cc.[62] Bronchospirometric studies will usually show a normal vital capacity on the uninvolved side, but a remarkable decrease on the affected side.[64, 65, 67] The maximal breathing capacity is reduced, but usually about 10 per cent higher than the vital capacity, so that the air velocity index exceeds unity.[63, 66, 67]

The following data have been noted: the residual volume may be normal, increased or decreased, with values between 49 and 161 per cent of the predicted volume, the total lung capacity is always less than normal even though the residual volume may be increased; and the intrapulmonary gas mixing, as measured by the 7 minute nitrogen wash-out method, is normal even in cases with an increased residual volume.[66] The increase in the absolute residual volume and the increased ratio of the residual volume to total lung capacity may suggest the presence of emphysema, but the normal intrapulmonary mixing index and the absence of obstructive ventilatory findings are not compatible with this diagnosis. It is interesting that the increase in the residual volume in a few patients with fibrothorax is not seen in patients with restriction due to thoracic deformity. Possible explanations are: (1) a lung which is not properly decreased in volume with expiration and (2) coexisting airway obstruction in the absence of the characteristic ventilatory pattern.

Arterial blood gases are generally normal in fibrothorax, but a decrease in oxygen saturation at rest is occasionally noted. The carbon dioxide content and partial pressure are usually increased when there is arterial oxygen unsaturation. These blood gas abnormalities may not appear unless the patient exercises.[61, 63, 65, 67]

Abnormalities of diffusion as measured with Riley's two level oxygen method have been observed in the study of a limited number of patients.[62] There is no increase in the venous admixture component of the alveolar arterial gradient, suggesting a parallel decrease in perfusion and ventilation of the affected lung.[61, 62, 66]

The determination of ventilation, oxygen uptake and vital capacity of each lung has been measured by means of broncho-spirometry. A reduction of all three parameters occurs on the affected side. The reduction in oxygen consumption is often greater than the reduction in ventilation. Following surgical removal of the pleural envelope, there is partial restoration of ventilation and vital capacity, with somewhat less improvement in oxygen uptake.

Hemodynamic studies have been performed so infrequently that generalizations are difficult.[65] In Feltman's case of bilateral calcific pleuritis the patient had polycythemia, hypoxia, hypercapnia, right ventricular hypertrophy and congestive failure. Complete pulmonary function tests revealed a severe restrictive ventilatory defect only, and severe respiratory acidosis, accentuated by oxygen administration was also present.[62] Severe cor pulmonale due to a restrictive ventilatory defect secondary to fibrothorax fortunately is extremely rare. When parenchymal disease is present, together with the pleural fibrosis, cardiac complications are more frequent.

With limited restoration of gas exchange in the involved lung despite the improvement in ventilation, the therapeutic value of decortication is most unsatisfactory. Accordingly, the careful selection of cases is paramount. A discouraging aspect preoperatively is the fact that even with complete physiologic and clinical studies it is not always possible to predict the outcome. In general, the prognosis is closely related to the duration of the process and the degree of underlying parenchymal disease.[61, 63, 65, 67]



FIG 3 —Lateral chest roentgenogram, pectus excavatum, illustrating posterior displacement of the xiphoid (Reproduced by permission of W B Saunders Co, from KOOP, C S Clin North America 36 1627, 1956)

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The normal pleura is paper thin, transparent, flexible and elastic. As thickening occurs, the pleural surfaces fuse and contract. In progressive cases, the intercostal spaces are narrowed,

the involved hemithorax reduced in size and the mediastinum is displaced to the affected side. With *pleural fibrosis, pulmonary* ventilation becomes increasingly impaired due to this restriction Constrictive calcific bilateral fibrosis may result in complete loss of thoracic motion and even restriction of the diaphragm.[62]

A striking correlation has been noted between functional impairment and the volume of the lung bound down by the abnormal pleural membrane. The vital capacity may be 50 to 65 per cent of the predicted volume.[64,66] In one case of bilateral fibrothorax the value was only 900 cc [62] Bronchospirometric studies will usually show a normal vital capacity on the uninvolved side, but a remarkable decrease on the affected side.[64,65,67] The maximal breathing capacity is reduced, but usually about 10 per cent higher than the vital capacity, so that the air velocity index exceeds unity.[63,66,67]

The following data have been noted. the residual volume may be normal, increased or decreased, with values between 49 and 161 per cent of the predicted volume, the total lung capacity is always less than normal even though the residual volume may be increased; and the intrapulmonary gas mixing, as measured by the 7 minute nitrogen wash-out method, is normal even in cases with an increased residual volume.[66] The increase in the absolute residual volume and the increased ratio of the residual volume to total lung capacity may suggest the presence of emphysema, but the normal intrapulmonary mixing index and the absence of obstructive ventilatory findings are not compatible with this diagnosis. It is interesting that the increase in the residual volume in a few patients with fibrothorax is not seen in patients with restriction due to thoracic deformity Possible explanations are. (1) a lung which is not properly decreased in volume with expiration and (2) coexisting airway obstruction in the absence of the characteristic ventilatory pattern.

Arterial blood gases are generally normal in fibrothorax, but a decrease in oxygen saturation at rest is occasionally noted. The carbon dioxide content and partial pressure are usually increased when there is arterial oxygen unsaturation. These blood gas abnormalities may not appear unless the patient exercises.[61,62,65-67]

Abnormalities of diffusion as measured with Riley's two level oxygen method have been observed in the study of a limited number of patients.[62] There is no increase in the venous admixture component of the alveolar arterial gradient, suggesting a parallel decrease in perfusion and ventilation of the affected lung [61,62,66]

The determination of ventilation, oxygen uptake and vital capacity of each lung has been measured by means of bronchospirometry. A reduction of all three parameters occurs on the affected side. The reduction in oxygen consumption is often greater than the reduction in ventilation. Following surgical removal of the pleural envelope, there is partial restoration of ventilation and vital capacity, with somewhat less improvement in oxygen uptake.

Hemodynamic studies have been performed so infrequently that generalizations are difficult.[65] In Feltman's case of bilateral calcific pleuritis the patient had polycythemia, hypoxia, hypercapnia, right ventricular hypertrophy and congestive failure. Complete pulmonary function tests revealed a severe restrictive ventilatory defect only; and severe respiratory acidosis, accentuated by oxygen administration was also present.[62] Severe cor pulmonale due to a restrictive ventilatory defect secondary to fibrothorax fortunately is extremely rare. When parenchymal disease is present, together with the pleural fibrosis, cardiac complications are more frequent.

With limited restoration of gas exchange in the involved lung despite the improvement in ventilation, the therapeutic value of decortication is most unsatisfactory Accordingly, the careful selection of cases is paramount. A discouraging aspect preoperatively is the fact that even with complete physiologic and clinical studies it is not always possible to predict the outcome In general, the prognosis is closely related to the duration of the process and the degree of underlying parenchymal disease.[61,63,65,67]

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Collapse of the Lung

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THE lung parenchyma with its 700 million alveoli in a sense is comparable to a soft, pliable honeycombed vessel or foam rubber sponge, in its normal physiologic state. The inner and outer surfaces are subjected to unequal pressures Because of its softness and flexibility the lung is maintained in an inflated condition by the weight (pressure) of atmospheric air through the open respiratory tract while it is held in apposition to the chest wall by the intrapleural pressure which is less than the atmospheric pressure This state is referred to sometimes as a partial vacuum. The surface area of the alveoli and their capillaries is identical in extent, namely 140 M² (about 1,000 square feet) Normally, the lung contains 8 per cent of the total blood volume on inspiration and from 5 to 7 per cent on expiration.

Collapse of the lung signifies reduction in volume to less than its status in forced expiration. Inasmuch as physiologic lung function is predicated upon patency of the alveoli and the air passages, infringement on or obliteration of these structures implies impairment of functional competence The extent of such functional insufficiency determines the degree of failure of the lung as the organ of respiration

Colloquially, "collapse of the lung," is synonymous with atelectasis The latter is thought of as airlessness of the lung The usage of both of these designations is rational and logical Other terms advocated for this condition are apneumatosis, apneumatic lung and detelectasis

Most cases of clinically significant collapse of the lung are acquired. Prior to birth the lung is in a collapsed state. This airless condition is present in the stillborn child Atelectasis of various degrees may be found in premature infants. It is attributable to weakness and functional incompetence of the respiratory muscles. Also, parts of the lung may remain in atelectatic condition because of undue softness of supportive bony structures of the thorax, immature, uninflatable lung lobules, underdevelopment or inadequate function of the respiratory center or depression of the latter by intracranial stasis or general hypoxia. It is known that in premature infants elastic fibers and capillaries of the lung are less developed than in the full-term child Respiratory physiology is influenced by the relatively few alveoli. Initiation and maintenance of respiration may be difficult under these circumstances. While the alveoli are collapsed, respiratory gas exchange takes place through the respiratory epithelium of the alveolar ducts Deranged and labile respiratory performance, with obviously low tidal air, calls for precautions and for provision of optimal environment as to temperature, oxygen and relative humidity Wilson and Farber expressed the view that in some of these instances incomplete expansion of the lung was due to cohesion of the moist surfaces of the lower respiratory tract [45]

Collapse of the lung may be encountered in infants born at term. In these cases, respiratory functional insufficiency may be brought about by eventration of, or developmental defects in, the diaphram with dislocation of abdominal organs into the thorax. Also, pulmonary collapse may result from a disturbance in the respiratory center following intracranial hemorrhage. Similar interference with the neural control of respiration is caused occasionally by intra-uterine anoxia or by depressant drugs given to the mother and transmitted to the fetus.

It takes several days after birth for the lung to become completely aerated This is so despite the rhythmic expansion and contraction of the fetal thorax, first observed by Patterson and Farr [31] These rhythmic motions are present a long time before term, and maintain a tidal flow of amniotic fluid through the pulmonary

air passages. Snyder and Rosenfeld demonstrated in experimental animals that India ink injected in the amniotic sac was detectable in the pulmonary alveoli in a short time.[40] In premature infants, expansion of the alveoli may take from two to three weeks In these cases, impending right heart failure is also present because of failure of the lung to expand and because of the slow change from a fetal to an infant type of circulation.

Recent studies have brought to light the fact that hyaline membrane disease—of which atelectasis is an integral part—is a significant cause of infant mortality. According to Simpson and Geppert, this condition was the cause of death in the newborn in 14 5 per cent of fatalities[39] Ninety per cent of these occurred in premature infants High incidence of this syndrome has been observed in babies delivered by cesarean section after labor complicated by placenta previa, in infants of diabetic mothers and in those with hypoxia. The extensive atelectasis is the result of occlusion of the alveoli and respiratory bronchioles by an eosinophile membrane. The latter develops through the interaction of aspirated amniotic fluid and pulmonary exudate of high protein content This was demonstrated experimentally. The following physiologic changes were recorded by Kalbert and his associates in infants with hyaline membrane syndrome[21] (1) increased minute volume of respiration resulting from an increased respiratory rate, (2) normal tidal air volume, (3) approximately normal carbon dioxide production, (4) alveolar ventilation within normal limits; (5) elevated functional dead space; (6) increased intra-esophageal pressure differences between inspiration and expiration; (7) administration of 60 per cent oxygen facilitated diffusion of oxygen across the alveolar membrane and increased the tidal volume Drorbaugh and his collaborators found great decrease in the compliance of the lung.[13] Recently, Briggs and Hogg reviewed necropsy findings in 110 liveborn infants and noted atelectasis in 16 (14.5 per cent), atelectasis with hyaline membrane in 37 (33 6 per cent) and lung collapse without hyaline membrane but of hyaline type in 9 (8.2 per cent).[7] They consider the latter a separate category because of the striking resemblance of histologic findings to that seen in association with hyaline membrane The respiratory distress in the two groups was of the same character. Hyaline-like atelectasis appears earlier than atelectasis with hyaline membrane. In the former group, the duration of life was up to 12 hours in 6, between 12 and 24 hours in 1 and between 25 and 36 hours in 2 In contrast, the highest incidence of hyaline membrane atelectasis occurred between 12 and 24 hours

One of the most frequent causes of lung collapse is pneumothorax On an etiologic basis three categories of this condition are distinguished. (1) spontaneous, (2) traumatic and (3) artificial. Although the term spontaneous pneumothorax (often called idiopathic or agnogenic) is firmly established, its usage can hardly be considered ideal in the light of modern observations The most common source of this condition is congenital cystic disease of the lung One of the possible sequelae of the latter is rupture of a subpleural cyst into the pleural cavity Another cause of spontaneous pneumothorax is primary constitutional inferiority of the visceral pleura. This may manifest itself in various ways; namely, as (1) congenital tissue defect, (2) increased fragility of the pleura, (3) failure of regenerative power of pleural mesothelium. In 1919, Berkley and Coffen first reported the occurrence of spontaneous pneumothorax which resulted from interstitial emphysema of the lung.[5] The ingenious experimental investigations of Macklin proved that air may escape from the alveoli to the supporting tissues which surround the pulmonary blood vessels[23] From here the air passes along the vascular sheaths toward the root of the lung where it enters the pleural space. Increased intrapulmonic pressure during cough, which may reach 200 mm. Hg (270 cm. H_2O), may cause a breakthrough of air by this route, provided the implicated structures are weakened Such localized structural weakness may be congenital or may develop as the result of inflammatory or degenerative changes. Air pockets within the substance of the lung are conventionally designated as bullae. They have been observed as a complication of measles whooping cough, chronic bronchitis, allergic

bronchial asthma, silicosis and lung abscess Excessive cough or a check-valve mechanism at their opening may increase the pressure within these bullae so that they break into one of the vascular sheaths.

Also, it is known that localized air pockets immediately beneath the visceral pleura (subpleural blebs) may break into the pleural space. Such subpleural blebs develop from pathologic changes in small bronchi and bronchioles in the proximity of the pleura. These changes attributable to inflammation, granulation, fibrosis, neoplasm, bronchospasm or accumulation of exudate may set up a check-valve mechanism. Depending on the consequent degree of pressure in these blebs, moderate or even slight cough may be sufficient to rupture them

Ehrlich and Schomer expressed the view that predilectional places may develop for rupture of the visceral pleura in consequence of its natural wear and tear [14] In normal respiration, the gliding of the lung in the thoracic cage provokes a continuous shedding and regeneration of the pleural mesothelium. When this regenerative process is defective, communication may be established between the adjacent bronchioles and the pleural cavity in consequence of the stretching force of cough.

Minute communications were demonstrated by Brock between peripheral alveoli and the subpleural areolar tissue and between the latter and the pleural space [8] He referred to these congenital anomalies as leaky lungs and porous pleura These defects may serve as portals of entry for air from the lung into the pleural cavity.

Bronchopleural fistula is a well known cause of spontaneous pneumothorax and lung collapse. Development of bronchopleural fistula may be brought about by inflammatory changes due to infection Also, it may result from infarction and neoplasms, primary or metastatic. Moreover, interference with normal blood circulation secondary to excessive fibrosis may be the source of degenerative changes which are followed by perforation of the pleura and pneumothorax. The incidence of lung collapse is comparatively low in so-called hypertrophic emphysema

Physiologic changes characteristic of lung collapse caused by spontaneous pneumothorax are best considered in the light of the basic functional features of the thorax and the lung. Respiratory excursions of the bony thorax and the diaphragm are responsible for the cyclic ventilatory motions of the lung. The centrifugal traction force of the intrapleural negative pressure holds the lung in apposition to the chest wall. Maintenance of the physiologic negativity of this pressure is essential for the transmission of the movements of the chest wall and the diaphragm to the lung. In spontaneous pneumothorax, with decrease in the negativity of the intrapleural pressure there is a proportionate decrease in the size and limitation in the ventilatory excursions of the lung. This can be accurately measured according to the formula originally devised by Hurtado and Fray for determining the respiratory excursions of the chest [20] X-ray films of the chest are taken at the end of inspiration and expiration with the patient in the upright position, at a distance of six feet. The margin of the collapsed lung is outlined and the lung area is measured with a planimeter The radiologic ventilatory formula is obtained as follows: radiologic area at maximum expiration over radiologic area at maximum inspiration times 100 The ratio is inversely proportionate to the amplitude of ventilatory excursions of the collapsed lung When the intrapleural pressure becomes neutral (atmospheric) in maximum inspiration, the collapsed lung is emancipated from the cyclic traction of the chest wall, becomes motionless and loses its respiratory function. The same holds true of spontaneous pneumothorax with pressure readings on the positive side (tension pneumothorax).

Pulmonary blood flow (hemodynamics) in collapse of the lung has been the subject of much controversy. Earlier investigators as Sauerbruch and Cloetta thought that there was an increased blood flow in the atelectatic lung [37] In acute massive atelectasis, for a short period of time, there is nearly normal perfusion of the nonventilated lung.[22] This condition is designated as "venous admixture" or "physiologic shunt". Bruns[9] and, later, Adams and his associates[1] definitely proved that the blood volume as well as the blood flow are decreased in col-

lapsed areas of the lung. According to the observations of Fine and Drinker the blood flow in the atelectatic lung is reduced by 16.9 per cent.[16] The reduction is explained on the basis of decrease in the size and loss of function of the affected lung tissue. Consequently, there is no change in the oxygen and carbon dioxide content of the blood passing through an atelectatic area. Similarly, Moore,[28] and also Berggren,[4] noted that the blood flow through areas of acute atelectasis was reduced by about 50 per cent during the first days and weeks. Subsequently, the blood flow showed a progressive decrease which was proportionate to the duration of atelectasis. The longer its duration, the greater the decrease. Adams and his associates demonstrated that the apparent increased vascularity of the lung which is found in massive atelectasis is in the nature of passive congestion rather than an active hyperemia.[1] The blood vessels are tortuous and the veins are distended. The alveolar walls are in approximation, and the alveoli contain white blood cells and serum. In chronic atelectasis, there is a gradual disintegration of the alveolar walls, with the formation of channels which connect the circulating blood with the alveoli. They found that in atelectasis of about four weeks' duration the circulating blood filled and re-expanded some of the alveoli, thus permitting the blood to reach the lumen of the smaller bronchioles. Moreover, they noted that when a lung with atelectasis of many months' duration was reinflated by pressure of 35 mm. Hg, the re-expansion was incomplete, and a lung lobe could be reinflated to only one-half or to two-thirds of its original size. The formation of a moderate amount of fibrous tissue was observed. The slow development of fibrosis may be attributable to the dual (pulmonary and bronchial) blood circulation. Fibrosis is bound to develop rapidly when atelectasis is complicated by infection.

Graham and his colleagues first introduced the term, "middle lobe syndrome."[19] It refers to atelectasis of the middle lobe with superimposed infection secondary to compression of the respective bronchus by enlarged tuberculous or nontuberculous regional lymph nodes. Accessory lower lobe on the right side (fourth lobe) occurs in from 15 to 20 per cent of normal individuals and accessory left lower lobe (third lobe) in 15 per cent. Atelectasis develops in them rather frequently, because their connecting bronchi become easily occluded.

Valuable pertinent data have been brought about through angiopneumography and cardiac catheterization. De Garvalho demonstrated diminished blood circulation in the collapsed lung in his clinical cases.[10] These findings parallel the observations of Macklin in experimental animals. He recorded pronounced shortening and narrowing of the pulmonary blood vessels in the atelectatic lung. With the aid of 70 per cent Diodrast as contrast medium, Bjoerk and Salen found no decrease in the caliber of the pulmonary artery and corresponding capillaries in acute experimental atelectasis.[6] The contrast medium passes through them and fills the pulmonary veins. When atelectasis persists, there is a continued decrease in the caliber of the corresponding pulmonary artery. After eight months of atelectasis its caliber is reduced to 60 per cent of that of the pulmonary artery of the opposite lung. In sustained atelectasis, there is a gradual decrease in the flow of contrast medium through the atelectatic parts of the lung until its complete cessation. From these findings they concluded that in the atelectatic lung the blood flow is shut off in the capillaries.

Physiologic changes in the collapsed lung parallel changes in the blood flow. In acute atelectasis, nonoxygenated blood returning through the pulmonary vein mixes with blood carried by the pulmonary vein of the normally ventilated lung. Consequently, the oxygen content of arterial blood in the systemic circulation is lowered. With protracted duration of massive atelectasis, with the associated cessation of its capillary blood flow, the oxygen content of blood in the greater circulation approaches normal.

Euler and Liljestrand found that when aeration is reduced in any area of the lung, there is a consequent local hypoxia.[15] This hypoxia, in turn, causes constriction of pulmonary arterioles in the same region which is not mediated through the autonomic nervous system. Obviously, vasoconstriction hinders normal

blood flow in the corresponding arterioles and precapillaries. Another significant consequence of localized hypoxia is increased capillary permeability. This is the most likely cause of associated pulmonary edema. Simultaneously, there develops thickening of the alveolar walls and closure of the interalveolar pores by alveolar transudate. This, of course, leads to further reduction of the locally available oxygen.

The train of events in experimental collapse of the lung after bronchial occlusion is worth remembering, because it reflects the experience of daily practice. Mendelsohn more than a hundred years ago first produced atelectasis experimentally by introducing foreign bodies into the bronchi[26] Following bronchial occlusion, absorption of the alveolar air by the blood stream results in atelectasis Coryllos and Birnbaum in 1932 showed that gases diffuse in the alveoli at a rate inversely proportionate to the square root of their density.[11] The density of the nitrogen molecule is 28, that of the oxygen molecule is 32 Their diffusion through the moist alveolar surface is predicated on their coefficient of solubility in the blood The solubility of various alveolar gases in 1 cc of water at body temperature is as follows oxygen, 0 024, nitrogen, 0 016, carbon dioxide, 0 592 Accordingly, the diffusion of carbon dioxide across the capillary membrane is 25 times greater than that of oxygen and 30 times greater than that of nitrogen. Other features of gas exchange pertaining to partial pressures and the speed of diffusion are described in Chapters 38 and 39.

The pertinent experimental studies of Coryllos and Birnbaum[11] are worth quoting·

> Immediately after successful obstruction the size of the occluded lung decreases without conspicuous change in its general shape, appearance and color Gradually it sinks toward the costophrenic sinus, whereas the other lung increases in size so that the heart [illegible] is markedly decreased (to about one-fifth or one-seventh its original size) Then there appear dark bluish brown patches scattered all over its surface without any predilection for the hilus or the peripheral portion of the lung After the great mass of the gas is absorbed, atelectasis advances rapidly, and within approximately one hour is complete

While these anatomic changes are taking place, the oxygen percentage of the alveolar air falls precipitously. Within 10 minutes it decreases from the normal 15 per cent to 5 or 6 per cent. It remains at this level until almost complete atelectasis ensues. Simultaneously, the alveolar carbon dioxide increases from its original level of 5 per cent to 6 per cent. Thus, an approximate equilibrium is established between the alveolar gases and the venous blood From then on, through further gas exchange, complete atelectasis results. Nitrogen plays an important role in the gradual development of this condition Due to the slow absorption of nitrogen into the blood, the absorption period of oxygen and carbon dioxide is prolonged

In areas of the lung with complete atelectasis, ventilatory and respiratory functions are absent. The hiluswsard retractility of peribronchial and perivascular radial elastic fibers is nil On the other hand, when lung collapse is incomplete, i e , the lung is in a state of abnormal deflation, its functional potentialities are determined by the following factors· (1) caliber and distensibility of the corresponding air passages; (2) presence or absence of intrapleural negative pressure; (3) transmissibility of intrapleural negative pressure to the partially collapsed lung, (4) respiratory expansibility of the collapsed lung, (5) integrity of the chest wall and respiratory muscles, including the diaphragm; (6) competence of pulmonary circulation.

Incomplete but pronounced atelectasis (subatelectasis) represents a hypokinetic and hypotensive state of the lung in reference to its elasticity It is associated with hypoxemia, carbon dioxide retention and respiratory acidosis, because the blood of the lesser circulation is passing through an area of respiratory incompetence (perfusion without gas exchange) When atelectasis becomes complete and all of the venous blood is passing from the right ventricle to the intact lung, these biochemical changes are reversed. This has been demonstrated by the experimental studies of Peters and Roos[32] and by the clinical observations of Beatrice and Alasia[3]

Compensatory function in the uninvolved parts of the lung develops proportionately to the oxygen deficit caused by partial lung collapse Several investigators[17, 25, 29, 34] have re-

TABLE 1.—*Studies in which the Effects of Pneumonectomy in Adults Have Been Evaluated*

Investigators	Ref No	Yr of Publication	No of Patients Studied
Cournand and Berry	11	1942	10
Birath, Crafoord and Rudstrom	4	1947	12
Burnett et al	7	1949	24
Cournand et al	13	1950	16
Gaensler and Strieder	18	1951	40
Friend	17	1954	15
McIlroy and Bates	24	1956	10
Burrows et al	8	1958	36

over-all resting pulmonary function The ventilatory equivalent for oxygen (minute volume/oxygen consumption) was often slightly increased, indicating a slight hyperventilation As a result of overinflation of the remaining lung, the vital capacity and total lung capacity were increased by 10 to 30 per cent over the predicted value for the one lung.

Some degree of distention, defined as increase in residual volume relative to normal, and increase in the ratio RV/TLC, was observed by Birath,[4] and by Cournand and associates.[11] Table 2, from the study of the latter authors, illustrates the correlation between distention and ventilatory efficiency, as in the studies on children.

Tolerance to exercise, tested in the first, fourth, fifth, seventh and eighth series, though reduced over preoperative values (the breathing reserve during exercise was about one-half normal) was usually satisfactory when the remaining lung was free from disease. Thus, dyspnea is not necessarily a consequence of pneumonectomy, except during heavy exertion

Reduction in Diffusing Capacity

For a given partial pressure gradient across the lung, the rate of diffusion of oxygen and carbon dioxide is proportional to the surface area of the lung and is therefore reduced by pneumonectomy.[15] Inasmuch as carbon dioxide is about 20 times more soluble in lung tissues and plasma than oxygen, its transfer across the lung is seldom seriously hampered as a result of impaired diffusion due to pulmonary resection. However, during severe exercise in human beings, the normal lung is pushed nearly to the

TABLE 2.—*Pulmonary Function After Pneumonectomy*

	Group I (Avg 7 cases)			Group II (Avg 9 cases)		
	Predicted	Observed	(Obs./Pred.) × 100	Predicted	Observed	(Obs./Pred.) × 100
1 Vital capacity, ml	1,916*	1,793	94%	1,960	2,450	125%
2 Residual volume, ml	576*	863	149%	685	1,163	170%
3 Total lung capacity, ml	2,492*	2,656	106%	2,644	3,630	137%
4 (RV/TLC) × 100	23%	32.5%	171%	26%	32%	123%
5 MBC, L./min	107	67	63%	108	75	69%
6 Intrapulmonary mixing (% N_2 after breathing O_2 7 minutes)	<2%	1.2%		<2%	1.4%	
7 Breathing reserve, L./min						
exercise	91	49	54%	88	53	60%
recovery	81	39	48%	78	47	60%
8 Arterial oxygen saturation, Avg (during rest and recovery after exercise)	96.1% (rest)	94.7% (recovery lowest = 88.1%)	1.4% (fall)	95.4% (rest)	93.1% (recovery lowest = 85%)	2.3% (fall)
9 $\frac{\text{Effective pul. blood flow}}{\text{Total pulmonary blood flow}} \times 100$	>94%	93.6%		>94%	93.7%	
10. $\frac{\text{Effective alveolar vent.}}{\text{Total ventilation}} \times 100$	>70%	68%		>70%	70%	

Modified from COURNAND, A., RILEY, R. L., HIMMELSTEIN, A., AND AUSTRIAN, R.: J. Thoracic Surg 19: 80, 1950.

* Predicted for one lung on same side.

blood flow in the corresponding arterioles and precapillaries. Another significant consequence of localized hypoxia is increased capillary permeability. This is the most likely cause of associated pulmonary edema. Simultaneously, there develops thickening of the alveolar walls and closure of the interalveolar pores by alveolar transudate. This, of course, leads to further reduction of the locally available oxygen.

The train of events in experimental collapse of the lung after bronchial occlusion is worth remembering, because it reflects the experience of daily practice Mendelsohn more than a hundred years ago first produced atelectasis experimentally by introducing foreign bodies into the bronchi.[26] Following bronchial occlusion, absorption of the alveolar air by the blood stream results in atelectasis Coryllos and Birnbaum in 1932 showed that gases diffuse in the alveoli at a rate inversely proportionate to the square root of their density [11] The density of the nitrogen molecule is 28, that of the oxygen molecule is 32 Their diffusion through the moist alveolar surface is predicated on their coefficient of solubility in the blood. The solubility of various alveolar gases in 1 cc. of water at body temperature is as follows oxygen, 0 024, nitrogen, 0 016, carbon dioxide, 0 592. Accordingly, the diffusion of carbon dioxide across the capillary membrane is 25 times greater than that of oxygen and 30 times greater than that of nitrogen Other features of gas exchange pertaining to *partial pressures* and the speed of diffusion are described in Chapters 38 and 39

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ported on constantly varying uneven ventilation, uneven distribution of tidal air as a normal physiologic phenomenon. There is a parallel uneven distribution of blood through the branches of the lesser circulation Such variable function of diverse parts of the lung explains in a large measure the facility of compensatory functional adaptation noted in cases with regional atelectasis. Even so, nonoxygenated, stagnating air of incompletely collapsed areas may be sucked into the normally functioning parts and thus vitiate the inflowing tidal air. In some of these instances, dyspnea disappears when atelectasis becomes complete and blood from the right ventricle bypasses collapsed lung tissue in its route to normally aerated regions

In massive atelectasis of one lung, there is a compensatory adaptation by the opposite lung The latter, if not diseased, after a short period of dyspnea, provides normal oxygen intake and carbon dioxide output Dale and Rahn recorded that experimental total occlusion of one main bronchus in dogs caused increased tidal volume in the opposite lung[12] This is brought about by adaptation of the chest wall and by shift of the mediastinum toward the blocked side, thus permitting enlargement of the open lung. The bronchospirometric studies of Pump in 23 men revealed that blocking the main bronchus of one lung resulted in increased functional residual capacity, increased tidal volume (when increase in functional residual capacity was pronounced) and increase in the respiratory rate in the open lung[13] In instances in which bronchial occlusion is the cause of lung collapse, the intrapleural pressure on the diseased side is highly negative With the loss of the balancing effect of equal pressures in the two pleural cavities, the healthy lung becomes distended and its inspiratory expansion is increased. This may lead to an unsatisfactory distribution of the tidal air with consequent functional impairment and dyspnea Bronchospirometry is the best means for the accurate determination of respiratory insufficiency of atelectatic areas.

Atelectasis may result from two types of bronchial occlusion: (1) stop-valve type of occlusion which prevents the inflow as well as the outflow of air; (2) check-valve type of occlusion which permits the egress of air but not the ingress. Either type may be encountered in pulmonary diseases in which there is thick, tenacious exudate in the lower air passages, such as severe bronchitis, bronchiolitis, pneumonia, including atypical pneumonitis, bronchiectasis and lung abscess In allergic bronchial asthma, massive atelectasis is rare, but lobular atelectasis is common Predilection to bronchial occlusion in patients with bronchial asthma is attributable mainly to edema of the bronchial mucosa, conglomeration of viscid secretions and to bronchospasm. The latter may be an adjunct cause of atelectasis in acute and chronic pulmonary infections, as well as in pulmonary hemorrhage when extravasated blood collects in some of the bronchi. Increased acidity of inflammatory exudate enhances bronchomuscular tonus and thus facilitates bronchospasm. Other well known causes of atelectasis are aspirated foreign bodies, benign and malignant tumors of the lung and other thoracic organs, intrathoracic cysts, enlarged thymus, substernal goiter, aneurysm, massive enlargement of mediastinal lymph nodes and large pleural and mediastinal effusion. Other space-occupying conditions which may cause atelectasis include cardiomegaly, pericardial effusion, paravertebral cold abscess and deformity of the chest wall.

In children, the bronchi are relatively narrow. Consequently, enlargement of hilar and peribronchial lymph nodes is more likely to result in complete lobar atelectasis than in adults In the latter age group, the bronchus leading to the right middle lobe and the one to the lingula of the left upper lobe are long and narrow and branch off at an acute angle. Because of this, atelectasis due to peribronchial lymph node enlargement is noted more often in these structures than elsewhere in the lung

Finally, mention should be made of atelectasis resulting from failure of normal nervous control of pulmonary ventilation. Such instances may be observed in trauma to the phrenic nerve or the vagus, in coma and in poliomyelitis Atelectasis is the most frequent complication of the latter, and it may lead to fatal termination Diseases of the central nervous system which directly or indirectly affect

the respiratory center are to be kept in mind in this connection. As stated before, tenacious secretions or mucous plugs may occlude bronchial passages either by a stop-valve or by a check-valve mechanism When the latter takes place in a manner so that inflow of air is prevented during inspiration while the outflow of air continues during expiration, rapid development of complete atelectasis follows.

Postoperative atelectasis was first reported by William Pasteur, an English physician, in 1910; he attributed it to a reflex inhibition of diaphragmatic excursions.[30] Scott assumed that postoperative atelectasis was due to spasm of the bronchioles or to a vasomotor disturbance associated with swelling of the bronchial mucosa.[36] Sante considered injury to the vagus and a consequent reflex spasm of the bronchial smooth muscles as the underlying cause of this condition.[35] De Takats and his associates demonstrated that traction on the cystic duct and pulling on the mesentery cause a vagal reflex which, in turn, results in bronchospasm and in an increase in the bronchial secretions.[43] Bilateral vagal section inhibits this effect One may consider autochton contraction of the lung parenchyma as a contributory factor. This possibility was postulated by Xalabarder who demonstrated action currents of the lung parenchyma independent of that produced by the peribronchial smooth muscles.[46] The validity of this concept has been confirmed by the experimental investigations of Sturm.[42] He observed atelectatic contraction of the alveoli as a reflex phenomenon elicited by stimulation of the pulmonary vascular system.

The lateral recumbent position does not predispose the lowermost lung to atelectasis. It is known that normally the dependent lung has a smaller lung volume at the end of expiration, with a concomitant higher position of the respective hemidiaphragm. Nevertheless, the dependent lung is subject to substantial cyclic variations corresponding to the two phases of ventilation. Bronchospirometric and x-ray studies of Vaccarezza and his associates, Rothstein and his co-workers, Gaensler and Miller and his colleagues; and Alix and Lozano proved that when a person is in lateral recumbency, there is an increase in the relative ventilation and oxygen uptake in the dependent lung.[19, 27, 33, 44] Moreover, the complemental air and "vital capacity" are greater.[2] At the same time, there is a decrease of its proportion or total functional residual air. Corroborative x-ray observations were reported recently by Mann.[25]

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Physiologic Effects of Collapse and Excisional Surgery

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THE first successful removal of one entire lung from a human being by Dr. Evarts Graham in 1933 stimulated research on the physiologic effects of pneumonectomy, with particular reference to: (1) *pulmonary reserve*, evaluated by ability to exercise, by dyspnea, and by means of objective tests of pulmonary function; (2) *pulmonary emphysema*, whether produced or aggravated by removal of the opposite lung, when no procedure such as thoracoplasty (which Dr Graham performed on his first pneumonectomy patient) is used to fill the space of the missing lung, (3) *pulmonary hypertension*, leading to cor pulmonale, whether produced or aggravated by pneumonectomy.

Pulmonary Reserve

As a result of many studies it is now clear that many postpneumonectomy patients are far from being pulmonary cripples and can exercise nearly as strenuously as normal people, the pulmonary reserve depending on the age at which pneumonectomy was performed, the degree of pulmonary distention and the condition of the remaining lung, with particular reference to emphysema The majority of patients studied were able to continue their normal work

Pneumonectomy During Childhood

Lester, Cournand and Riley studied three children aged 9, 12 and 14 years old in whom pneumonectomy was performed at the ages of 6, 10 and 11 years respectively[22] The exchange of oxygen and carbon dioxide was entirely normal at rest The total lung capacity and vital capacity were found to have increased by 25 to 40 per cent above the predicted normal values for one lung. The maximum breathing capacity (MBC) was only moderately reduced, being 62, 75 and 78 per cent of predicted values. One of the subjects performed strenuous exercise even longer than normal children, the other two for almost as long. The breathing reserve, (MBC—resting minute volume) was reduced by half during exhausting exercise in two of the operated children, though not at all in the third. There was no fall in oxygen saturation of arterial blood, collected shortly after exercise.

The children, as noted above, were studied again five years later,[12] together with a fourth child In two of the cases, there was evidence of distention of the lung, as indicated by a marked increase in the ratio of residual volume to total lung capacity This was correlated with impaired pulmonary function, as indicated by a reduction of the MBC to 55 per cent of normal as compared to 83 and 75 per cent in the children without pulmonary distention, and by a fall in arterial oxygen saturation during severe exercise of approximately 14 per cent, as compared with a 5 and 6 per cent fall in the children without distention.

Even though the residual volume was increased in 5 of the 10 subjects studied by Peters and associates,[29] 1 to 13 years after pneumonectomy performed in childhood, all but one subject, in whom there was disease in the remaining lung, could perform moderate exercise for seven minutes, and without fall in oxygen saturation The authors emphasized the importance of physical training, the best performance being in 2 patients who had worked hard to overcome the handicap. One young woman had succeeded in becoming a champion gymnast, and a young man had become a construction worker employed at an altitude of 5,000 feet

Pneumonectomy in Adults

TABLE 1 presents some of the investigators, together with the date of publication and number of patients studied, who have evaluated the effects of pneumonectomy in adults. On the whole, there was remarkably little change in

TABLE 1.—*Studies in which the Effects of Pneumonectomy in Adults Have Been Evaluated*

Investigators	Ref No	Yr of Publication	No of Patients Studied
Cournand and Berry	11	1942	10
Birath, Crafoord and Rudstrom	4	1947	12
Burnett et al	7	1949	21
Cournand et al	13	1950	16
Gaensler and Strieder	18	1951	40
Friend	17	1954	15
McIlroy and Bates	21	1956	10
Burrows et al	8	1958	36

over-all resting pulmonary function. The ventilatory equivalent for oxygen (minute volume/oxygen consumption) was often slightly increased, indicating a slight hyperventilation. As a result of overinflation of the remaining lung, the vital capacity and total lung capacity were increased by 10 to 30 per cent over the predicted value for the one lung.

Some degree of distention, defined as increase in residual volume relative to normal, and increase in the ratio RV/TLC, was observed by Birath,[4] and by Cournand and associates.[13] Table 2, from the study of the latter authors, illustrates the correlation between distention and ventilatory efficiency, as in the studies on children.

Tolerance to exercise, tested in the first, *fourth, fifth, seventh and eighth series, though* reduced over preoperative values (the breathing reserve during exercise was about one-half normal) was usually satisfactory when the remaining lung was free from disease. Thus, dyspnea is not necessarily a consequence of pneumonectomy, except during heavy exertion.

Reduction in Diffusing Capacity

For a given partial pressure gradient across the lung, the rate of diffusion of oxygen and carbon dioxide is proportional to the surface area of the lung and is therefore reduced by pneumonectomy.[15] Inasmuch as carbon dioxide is about 20 times more soluble in lung tissues and plasma than oxygen, its transfer across the lung is seldom seriously hampered as a result of impaired diffusion due to pulmonary resection. However, during severe exercise in human beings, the normal lung is pushed nearly to the

TABLE 2.—*Pulmonary Function After Pneumonectomy*

	Group I (Avg 7 cases)			Group II (Avg 9 cases)		
	Predicted	Observed	(Obs/Pred) × 100	Predicted	Observed	(Obs/Pred) × 100
1. Vital capacity, ml	1,916*	1,793	94%	1,960	2,450	125%
2 Residual volume, ml	576*	863	149%	685	1,163	170%
3 Total lung capacity, ml	2,492*	2,656	106%	2,644	3,630	137%
4 (RV/TLC) × 100	23%	32 5%	171%	26%	32%	123%
5 MBC, L/min	107	67	63%	108	75	69%
6 Intrapulmonary mixing (% N_2 after breathing O_2 7 minutes)	<2%	1 2%		<2%	1 4%	
7 Breathing reserve, L/min						
exercise	91	49	54%	88	53	60%
recovery	81	39	48%	78	47	60%
8. Arterial oxygen saturation, Avg (during rest and recovery after exercise)	96 1% (rest)	94 7% (recovery lowest = 88 1%)	1 4% (fall)	95 4% (rest)	93 1% (recovery lowest = 85%)	2 3% (fall)
9 $\frac{\text{Effective pul blood flow}}{\text{Total pulmonary blood flow}} \times 100$	>94%	93.6%		>94%	93 7%	
10 $\frac{\text{Effective alveolar vent}}{\text{Total ventilation}} \times 100$	>70%	68%		>70%	70%	

Modified from COURNAND, A, RILEY, R L, HIMMELSTEIN, A, AND AUSTRIAN, R J Thoracic Surg 19: 80, 1950

* Predicted for one lung on same side.

limit of its diffusing capacity for oxygen, hence a reduction in the latter might be expected to lead to hypoxia during activity, with dyspnea resulting from stimulation of the *carotid and aortic chemoreceptors, which reflexly "drive"* the respiratory center

It is natural then, that the effects of pulmonary resection on the *diffusion* of gases *across* the lung have been evaluated in experimental animals and in patients.

Dogs have been found to have a large pulmonary reserve, and diffusion, as well as *other pulmonary* functions—adequate even after extensive resection Longacre and Johansmann found that dogs could tolerate severe hypoxia at rest after pneumonectomy and could also perform severe exercise, almost as well as control animals [23]

Animals from whom all of the lung but the right upper lobe was removed, representing about 15 per cent of the original, led active lives for prolonged periods.[29] In such animals, there is little pulmonary reserve, as evidenced by cyanosis during exercise, and by an approximately 80 mm. increase in alveolar-arterial oxygen diffusion gradient in going from rest to severe exercise [27]

Following removal of 68 per cent of the original lung, Williams and others could detect *no* increase in alveolar-arterial oxygen tension gradient at rest,[37] additional evidence for the dog's great margin of safety for diffusion.

Though the pulmonary reserve in human beings is less than in dogs, there was only a slight fall in arterial oxygen saturation during exercise in the postpneumonectomy patients studied by Cournand and associates (TABLE 2). These data, which are fairly typical of the several other series of patients, indicate that the diffusing capacity for oxygen is adequate for moderate activity, provided the remaining lung is normal

The adequacy of function of the remaining lung depends, as stated above, on the age at which pneumonectomy is performed Using the technic of Lilienthal and Riley for measuring diffusing capacity of the lung for oxygen (D_{Lo_2}), Cournand's group[12] found normal values (20, 25 and 25) in three patients in whom pneumonectomy had been performed in childhood. By contrast, two with operations performed *in middle age had diffusing capacities* (D_{Lo_2}) *of* 14 and 16. These values are two-thirds to three-quarters of the normal figure of 21, the average value for the D_{Lo_2} of 6 normal subjects. The increase in pulmonary blood flow which accompanies exercise has been shown to increase the pulmonary diffusing capacity.[25] Since the resting blood flow through the remaining lung is approximately doubled after pneumonectomy, one could *partially account for the higher* than *predicted diffusing capacity* observed in all five of these patients. The lungs of the younger group would in addition be of the type described by Bremer in animals.[5] There is actual regeneration of new alveoli, as evidenced by the appearance of tubular *sprouts* developing from terminal alveoli and by a lengthening of the bronchial tree *distally* so as to form new primary lobules This process, identical to the growth and development of the lung *in normal young* people or animals, would provide a greater surface for diffusion. However, when pneumonectomy is performed after puberty, the lung which is left expands by simple dilatation of all parts of the lobules, the available surface for diffusion being little increased

Using the "Bates II" carbon monoxide method for measuring diffusing capacity (D_{Lco}), McIlroy and Bates[24] found the D_{Lco} to average 7 4 at rest (normal for both lungs = 17) and 11.3 during exercise (normal = 28 8) in 10 patients aged 39 to 63 The fact that D_{Lco} was less than half normal indicates that the remaining *lung was not entirely* free of disease.

Pulmonary Emphysema and its Relation to Pneumonectomy

Many experiments have been performed on animals, chiefly dogs, to determine whether the overinflation of remaining lung which follows *pneumonectomy* (unless steps such as thoracoplasty are taken to prevent it) may lead to true pulmonary emphysema. Proof of the presence of the latter requires fulfillment of the criteria established in 1861 by Rokitansky, namely: (1) dilatation of pulmonary alveoli; (2) obliteration of capillaries; (3) fragmentation of elastic fibers in alveolar septa; and (4) rupture of alve-

olar walls. Though Rienhoff,[30,31] and Behrend and Mann[2] concluded that emphysema does not follow pneumonectomy in dogs, others have reported microscopic changes highly suggestive of that condition. Thus, Phillips, Adams and Hrdina[29] observed stretching and fragmentation of the alveolar walls after a combination of multiple lobectomy and atelectasis produced in other lobes by stenosing their bronchi. They called this "compensatory emphysema" because it partially filled the vacant space. "Patchy" and "marginal" emphysema in dogs were described by Paine[26] as the result of overdistending the lung by reefing the diaphragm. Longacre and Johansmann[23] found overdistention of alveoli, ruptured alveolar walls, clubbing of alveolar septa, a suggestion of fragmentation of elastic fibers, and a slight loss of elastic recoil of the lung, changes they consider representative of true interstitial emphysema

The recent studies of Lategola show that following multiple lobectomy the degree of inflation of remaining lobes of the lung depends on their location.[21] Thus, the right upper lobe was overinflated and underperfused, whereas the left lower lobe was underinflated and overperfused, its functional residual capacity actually being reduced below normal, when all but these two lobes were removed

Detection of Emphysema by Pulmonary Function Tests

Some of the tests listed in Table 2 are of particular value in detecting the presence and severity of pulmonary emphysema. Of the lung volumes, the vital capacity has been found to be of little value in this respect, but the residual volume and total lung capacity are particularly important, since they indicate distention, together with the ratio RV/TLC, which is increased in emphysema as the lung loses its elasticity and becomes chronically overinflated at end-expiration There is evidence for distention in the average data of Table 2, the residual volume expanding in greater proportion than the entire lung (lines 2, 3 and 4). Similar average data were obtained by Birath,[4] by Gaensler and Strieder,[15] and by Friend [17] In the latter two series, the total and residual lung volumes increased gradually by as much as 10 per cent during the first three months after pneumonectomy, but did not increase subsequently, suggesting that the size of the lung had become stabilized without the development of emphysema.

Should true interstitial emphysema exist in addition to simple distention, the MBC and breathing reserve would be reduced more than with pneumonectomy alone, due largely to the presence of bronchiolar obstruction, a frequent if not universal accompaniment of this disease. Such marked reductions have not usually followed pneumonectomy, the data of Cournand et al. being fairly representative of several series (Table 2).

Measurement of intrapulmonary mixing (gas distribution) was evaluated in this same group in terms of the Darling test,[11] in which per cent alveolar nitrogen is measured after breathing oxygen for seven minutes, less than 2 per cent N_2 being considered satisfactory for patients following pneumonectomy Average values are seen to be within normal limits

With reference to gas distribution, as evaluated by the nitrogen washout curve technic,[16] only slight impairment was found in a series of postpneumonectomy patients studied by Burrows et al [8]

The ratio of effective pulmonary blood flow to total pulmonary blood flow, (line 9, Table 2) expressed as per cent, represents a measure of the relative quantity of blood perfusing poorly or nonventilated alveoli, and when subtracted from 100 per cent gives the percentage of right-left venous admixture, often high in emphysema Second, the ratio of alveolar to total ventilation, expressed as per cent, is a measure of the ventilation of poorly or nonperfused alveoli, and when subtracted from 100 indicates the proportion of the tidal volume occupied by the physiologic dead space, also high in emphysema Since average values for both of these expressions are within normal limits (Table 2), the ventilation-blood flow relations are in general little disturbed.

In summary, the tests referred to tend to rule out the widespread occurrence of obstructive interstitial emphysema in the postpneumonectomy patients studied, and several workers state independently that the degree of

pulmonary overdistention produced by pneumonectomy is not likely to lead to true emphysema in normal young individuals. In older individuals, pneumonectomy probably hastens the progress of preexisting emphysema

Agreement is fairly uniform that thoracoplasty is not necessary to prevent overdistention after pneumonectomy except when there is emphysema preoperatively, or rapid progression of distention postoperatively In the series of Cournand and associates,[13] the end results of thoracoplasty were only moderately favorable.

Though overdistention appears not to produce true obstructive emphysema, it may lead to what McIlroy and Bates call "a different type of emphysema, without bronchitis and bronchiolar obstruction,"[24] or what Cournand et al refer to as "nonobstructive emphysema "[13] Support for such an entity is provided by the work of Shepard and co-workers [34] Though the loss in efficiency of pulmonary function is surely less than in true emphysema, consideration should be given to the suggestion of Gaensler and Strieder,[18] and of others, that improved means for preventing pulmonary distention should be sought, such perhaps as plastic sponge plombage

Factors Producing Dyspnea After Pneumonectomy

It is surprising that dyspnea does not always follow pneumonectomy, since several factors are tending to produce it. Thus, not only may ventilatory function and diffusing capacity be reduced, but the work of breathing may be increased [24] By measuring intra-esophageal pressure, which approximates intrapleural pressure, simultaneously with volumes of air moved per unit time, McIlroy and Bates[24] calculated pulmonary compliance, expressed in liters of air/cm. H_2O, and inspiratory airway resistance, in cm. H_2O/L./sec., and from these data calculated the work done per breath The averaged results are given in TABLE 3, modified from their publication.

The lung is "stiffer," (less easily inflated) after pneumonectomy because it is distended to the point at which a given increase in volume requires a greater change in pressure than normal The airway resistance is increased because the tidal volume must flow through the bronchial tree of only one lung, requiring additional pressure to overcome flow The work of breathing (= intrapleural pressure change times volume of air breathed) is thus increased, tending to fatigue the patient and contribute to dyspnea.

Increased stiffness of the lung, by stimulating the vagal stretch receptors involved in the Hering-Breuer respiratory reflexes, has long been associated with an increase in respiratory rate, an added source of dyspnea McIlroy and Bates mention a surprising lack of tachypnea during exercise in one patient in whom it was believed that the vagal endings to the remaining lung were cut at the operation, thus abolishing these reflexes

PULMONARY HYPERTENSION

Atelectasis or Collapse of the Lung

Varying degrees of decreased inflation of the lung to complete airlessness (atelectasis) may occur in the following conditions (a) following

TABLE 3 —*Mechanics of Breathing and Pulmonary Diffusing Capacity Following Pneumonectomy*

	Minute Volume (L./min)	Compliance (L /cm H_2O)	Mean Inspiratory Resistance (cm H_2O/ L./sec)	Inspiratory Work (Kg /min)	End Expiratory Level (cm H_2O)	O_2 Uptake (L /min)	Diffusing Capacity-D_{CO}
Normal values—(two lungs) at rest		0 12-0 33	1 5-4 0	0 2-0 5	0 to −5	—	Mean = 17 0 Range = 10 0-25 0
Avg 10 patients							
at rest	9 85	0 053	8 97	0 835	−7 37	—	7 39
during exercise	22 6	0 043	5 54	3 648	−7 64	0 992	11 26 (predicted ½ Normal = 14 4)

Modified from McILROY, M B, AND BATES, D V Thorax *11* 303, 1956

surgical procedures due to bronchial obstruction, (b) spontaneous pneumothorax, (c) collapse therapy for pulmonary tuberculosis either by pneumothorax or by thoracoplasty and (d) bronchial stenosis with total atelectasis of the lung caused by injury or disease.

Circulation of blood through the lung goes hand in hand with ventilation of the lung. As the lung becomes less inflated, resistance to blood flow increases with resultant diminution of volume flow through the involved lung. As deflation continues until a state of atelectasis develops, an increasing proportion of the total blood flow is shunted through the remaining aerated lung. When the uninvolved lung is normal in structure and function, the reserve is adequate to permit sufficient blood flow to maintain normal cardiac output This is especially true in children and young adults In collapse of the lung, these individuals during the resting state maintain normal right ventricular and pulmonary artery pressures However, on exercise when there is a demand for increased cardiac output, these pressures will become somewhat elevated due to the decreased cross sectional vascular bed of the lungs In most normal individuals, however, this alteration is insufficient to handicap the individual or change his way of life, excepting that extreme forms of exercise or exertion are avoided.

Massive collapse of the lung due to bronchial obstruction following surgical procedures or trauma frequently involves a combination of reduced lung capacity and physiological shunting of blood through the lung without aeration. This not only reduces functional lung capacity and thus pulmonary ventilation but also produces some degree of hypoxia with resultant dyspnea and, at times, cyanosis Not infrequently, the atelectasis is patchy in distribution, the amount of physiologic shunt varying from period to period according to the effectiveness of therapy for clearing the tracheobronchial tree. This is usually accomplished by catheter aspiration but, if unsuccessful, bronchoscopy or tracheostomy are indicated. Liquefaction of the bronchial secretions by the use of humidified air, potassium iodide or ammonium chloride are helpful in eliminating bronchial secretions and thus avoiding or effectively managing this serious complication Oxygen therapy and cardiac support are valuable aids when indicated. When there is decreased pulmonary reserve due to existing disease or deteriorating processes, resistance to blood flow through the remaining aerated lung may be significantly increased with resultant pulmonary hypertension. The importance of avoiding postoperative massive atelectasis with accompanying degrees of shunting is thus apparent.

Spontaneous pneumothorax occurs more commonly in cases of marked deterioration of the lungs containing blebs and bullae. The pathology may be general or localized in distribution Pulmonary hypertension and blood oxygen desaturation occur in varying degrees, and in severe cases may lead to fatality. This is usually on the basis of a combination of inadequate pulmonary function, hypoxia due to physiologic shunting and a sudden increased work load placed on the right heart due to increased pulmonary resistance. Marked dyspnea and cyanosis may occur and require immediate oxygen therapy and removal of pleural air by constant suction. Definitive therapy will vary according to the distribution of the degenerative process. In the diffuse bilateral type of involvement, medical management aimed at improving pulmonary function and prevention of infection are of paramount importance In the localized type, surgical excision of the involved part is indicated.

Collapse therapy for tuberculosis In advanced stages of this infection, which usually is bilateral in distribution, increase in pulmonary resistance to blood flow develops both due to the active pathology as well as fibrosis resulting from healing of the disease Thus, various degrees of pulmonary hypertension may be required for maintaining adequate cardiac outputs. The additional alteration in pulmonary as well as circulatory function produced by surgical collapse procedures in such patients will vary according to the pulmonary reserve In most cases, the effect of surgical collapse will be greater on ventilatory and diffusion functions than on pulmonary circulation. If pulmonary hypertension appears to be a major factor of concern, collapse therapy may have a

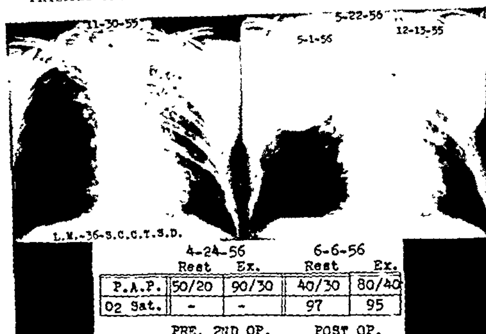


FIG 1 —L M , age 36 X rays of the chest before and following bilateral extrafascial paraffin collapse therapy for bilateral pulmonary tuberculosis Note that the resting as well as exercising pulmonary artery pressures were markedly elevated before surgery and that there was no

lead a sedentary type of life.

ite advantage over resectional therapy in pulmonary tension will be less increased ollapse than by resection (FIG. 1). By measg pulmonary artery pressures through iac catheterization, a decision regarding two types of treatment may be reached.

ı *total atelectasis* of one lung following achial stenosis by injury in children and ng people the physiologic alteration of both tilatory and circulatory functions is so well rated that resultant symptoms are minimal. remaining uninvolved lung becomes overtended and tends to herniate across the diastinum, occupying a portion of the pleural ity on the involved side (FIG. 2). In such tances, the lung resistance to blood flow is t increased materially and thus little addinal work is placed on the right heart Alough the resistance to blood flow through the electatic lung is considerable, a physiologic unt through this lung is present. As deterined by measurement in dogs with one lung llapsed this represents approximately 15 per cent of the normal flow. The resultant hypoxia however is insufficient to produce cyanosis and the level of oxygen saturation usually does not fall below 90 per cent. The area of bronchial stenosis has been removed surgically and the airway re-established in dogs, in children with stenotic bronchi following injury and in patients with pulmonary tuberculosis. The reaerated lung under these circumstances appears to be fairly normal on microscopic examination and exhibits good diffusion function. However, re-aerated lung tissue has a greater resistance to blood flow than does normal lung This has been demonstrated in dogs by obstructing the blood flow to the normal lung after the involved side has been re-aerated. The pulmonary artery pressure in the side which has been re-aerated becomes elevated by as much as 50 per cent in the resting state whereas the pulmonary pressure in the uninvolved side is not affected or very little affected by obstructing the blood flow through the re-aerated side.[3]

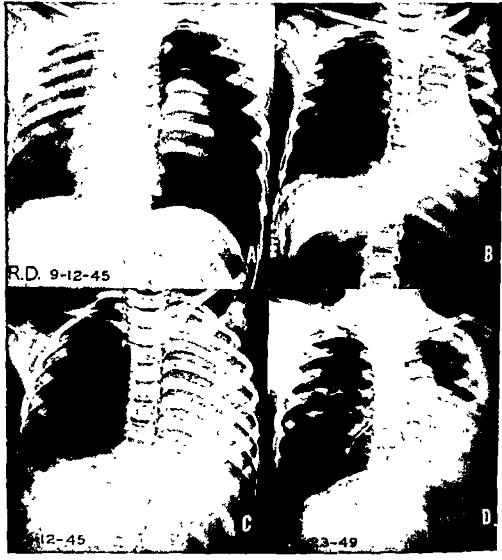


FIG 2 —R D, age 5 (at time of injury) (A) X-ray of the chest following a traumatic injury resulting in spontaneous pneumothorax with collapse of the left lung and shift of the mediastinum toward the right Much dyspnea and some cyanosis were present until the intrapleural air was removed by continuous suction (B) X-ray of chest showing a marked shift of the mediastinal structures toward the left and with some pneumothorax persisting The patient at this time was largely asymptomatic (C) X-rays showing further shifting of mediastinal structures to the left with herniation of the right lung into the left chest. The pneumothorax has disappeared and the left lung is completely atelectatic (D) Bronchograms showing complete stenosis of the left primary bronchus and with the right lung shifted well over into the left chest, the left lung remaining completely atelectatic and the heart being rotated posterolaterally When this picture was made three and one-half years following the accident, the patient was having no symptoms at rest or during exercise

Resection of the Lung

Pulmonary resection became safe and received wide usage during the fourth decade of this century. At the beginning of this period, when little physiologic study had been made for guidance, surgery advanced somewhat by trial and error. Graham once posed the question "how little lung tissue is life compatible?"[9, 10, 19] In children and in young adul[ts] either bilateral or unilateral resection of t[he] lung when limited to 50 per cent produces litt[le] or no alteration of pulmonary circulation f[or] maintaining adequate cardiac output and ther[e]fore is well tolerated. Pulmonary artery pre[s]sures are somewhat elevated by exercise b[ut] appear to cause little alteration in the child

activities. The pleural space remaining following pneumonectomy is occupied largely by overdistended lung of the remaining uninvolved side. Since overdistention of normal pulmonary tissue does not increase resistance to the flow of blood, the work of the right heart is little altered.

The effects of pulmonary resection on the pulmonary circulation in adults are largely influenced by previous disease or degenerative processes. Deterioration of pulmonary structure as well as reserve increases gradually between the age of 40 and 60 years. With greater amounts of pathologic change, pulmonary resistance to blood flow increases with resultant pulmonary hypertension. The effect of this change is much more noticeable during exercise than while at rest. When a lung has been largely destroyed by far advanced tuberculosis, alteration in pulmonary circulation is brought about gradually and is usually fairly well tolerated. Resection of such a lung is much less likely to increase the burden of the right heart than if the preoperative status of the circulation was less altered.

Total pneumonectomy in patients under 50 years of age is usually well tolerated and results in little elevation of right heart pressure. This is well reflected in the mortality rate for pneumonectomy for carcinoma of the lung which is currently 2 to 5 per cent in patients of that age group. Following pneumonectomy, exercise is moderately well tolerated according to the functional state of the remaining lung. Demands for increased cardiac output by exercise place some strain on the right heart as indicated by varying degrees of pulmonary hypertension. Under the age of 50 however, adjustment to the condition can usually be made and relatively normal activities as well as working conditions may be well tolerated.

Between the ages of 50 and 60, increased deterioration of the lung occurs, and thus the effect on pulmonary circulation following the removal of one lung may be considerably increased. This is reflected in the mortality rate of pneumonectomy which varies from 15 to 25 per cent for patients over 60 years of age. With increased deterioration of the lung, pulmonary resistance to circulatory flow gradually increases. Pulmonary artery pressures measured either prior to or at the time of surgery are frequently elevated over the normal level by as much as 50 to 100 per cent. If these measurements are made prior to surgery, at rest and during exercise, some indication as to the tolerance level of resection may be obtained, and thus aid in planning surgical care.[4, 25, 26] Patients whose pulmonary hypertension reaches 50 to 75 per cent above normal prior to surgery and is further elevated another 50 per cent following pneumonectomy are unlikely to survive surgery. Immediately following surgery, pulmonary hypertension may be further increased by patchy atelectasis and accompanying hypoxia resulting from inadequate elimination of bronchial secretions. At the present time, cor pulmonale due to cardiopulmonary insufficiency is the most frequent cause of death following pneumonectomy for carcinoma of the lung. Due to this hazard less extensive resections such as lobectomy and bilobectomy are preferred for malignant tumors in the peripheral portion of the lung where such operations appear to remove all of the tumor-bearing tissue.

Late effects of pulmonary resection. This problem was studied in a group of 30 patients ranging in age from 23 to 74 years. Three of these patients had bilateral pulmonary resection, one had a left upper lobectomy and the remaining 25 had a total pneumonectomy. The studies were made from 3 weeks to 15½ years following the above surgical procedures. The patients were hospitalized for a period of two days during which time complete pulmonary function studies as well as pulmonary artery pressures and cardiac output studies were made, the latter two at rest and during exercise. The *functional capacity* of each patient at the time of study was determined by history and clinical evaluation, and classified according to the New York Heart Association as follows: Class I, no limitation of physical activity; Class II, slight to moderate limitation of physical activity, Class III, moderate to great limitation of physical activity, and Class IV, unable to carry on any physical activity without discomfort. FIGURES 3–6 show the chest roentgenogram and function studies of representative patients in these functional classes. FIGURE 7 *graphically*



FUNCTIONAL CLASS I.

T.L.C.	3.85 L.	
V.C.	2.05 L. (68%)	
R.V.	1.5 L.	
M.B.C.	57.0 L./min. (60%)	
1 sec V.C.	74%	
	Rest	Exer.
Pulm.Art.Press.	$\frac{25}{8}$ (14)	$\frac{41}{17}$ (25)
Art. O_2 Sat.	95%	97%
Pulse Rate	110.0	146.0
O_2 Consumption	235.0	579.0
Cardiac Output (L./min.)	5.5	9.3

Fig 3 —Case 13, J K, 3 years post-left pneumonectomy T L C, total lung capacity, V C, vital capacity—per cent of normal predicted for subject with two lungs, R V, residual volume, M B C, maximum breathing capacity—per cent of predicted value for a normal chest with both lungs, 1 sec V C, per cent of the vital capacity expired in the first second, Pulm Art Press, pulmonary artery pressures (mm Hg) Mean pulmonary artery pressure in parentheses, Art O_2 Sat, arterial oxygen saturation, O_2 Consumption, oxygen consumption (ml /min)



FUNCTIONAL CLASS II.

T.L.C.	2.4 L.	
V.C.	1.5 L. (54%)	
R.V.	0.9 L.	
M.B.C.	36.0 L./min. (33%)	
1 sec V.C.	62%	
	Rest	Exer.
Pulm.Art.Press.	$\frac{22}{8}$ (13)	$\frac{39}{15}$ (23)
Art. O_2 Sat.	98%	95.5%
Pulse Rate	92.0	112.0
O_2 Consumption	218.0	542.0
Cardiac Output (L./min.)	6.25	8.26

Fig 4 —Case 1, E B, 8 years post-right thoracoplasty, 4 years post-right pneumonectomy. (Use same key as in Figure 3)



FUNCTIONAL CLASS III.

T.L.C.	2.8 L.	
V.C.	1.2 L. (34%)	
R.V.	1.6 L.	
M.B.C.	31.0 L./min. (34%)	
1 sec V.C.	71%	
	Rest	Exer.
Pulm.Art.Press.	$\frac{38}{13}$ (21)	$\frac{56}{30}$ (39)
Art. O_2 Sat.	94%	95%
Pulse Rate	88.0	116.0
O_2 Consumption	206.0	591.0
Cardiac Output (L./min.)	3.2	6.3

Fig 5.—Case 25, L R, 15½ years post-right pneumonectomy and thoracoplasty. (Use same key as in Figure 3) Patient had to discontinue work and leads a very sedentary type of life



FUNCTIONAL CLASS IV.

T.L.C.	5.66 L.	
V.C.	2.5 L. (75%)	
R.V.	3.03 L.	
M.B.C.	32.0 L./min.(43%)	
1 sec V.C.	46%	
	Rest	Exer.
Pulm. Art. Press.	$\frac{75}{35}$(48)	$\frac{112}{45}$(67)
Art. O_2 Sat.	96%	90%
Pulse Rate	84.0	92.0

Fig. 6.—Case 29, J S., 7½ years post-left pneumonectomy. (Use same key as in Figure 3.) Patient is now a pulmonary cripple and cannot walk across the room without dyspnea

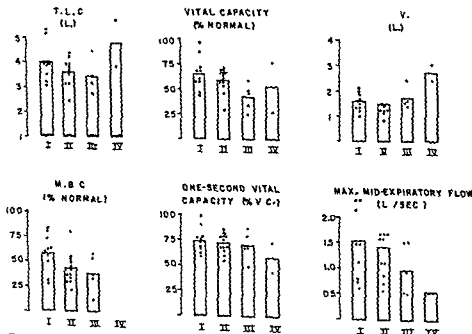


Fig 7.—Pulmonary function studies after extensive pulmonary ... patients in each group (See text for definition)

relates the ventilatory and lung volume measurements of these 30 patients to their functional ... the pulmonary artery systolic pressure, and the arterial oxygen saturation. There appeared to be a rough inverse correlation between the age of the patient at the time of the study and his functional capacities A more striking relationship, however, was found between the age of the patient at the time of his surgery and his resultant functional class: The older the pa-

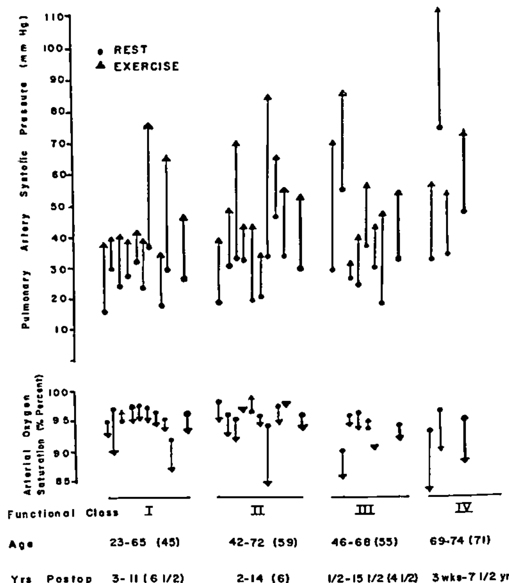


FIG 8 —Circulatory studies after extensive pulmonary resection (28 patients) Pulmonary artery pressures and arterial oxygen saturations during rest and exercise, grouped according to the patient's functional class The lighter vertical lines represent the changes during exercise for each subject The heavier vertical lines at the extreme right of each group represent the averages for the groups Functional Class—see text for definition Age—the range of ages of patients within each group and the average age for the group Yrs Postop , the range of the number of years after surgery for the patients in each group and the average for the group With the exception of four cases—one in each functional class—elevation of pulmonary artery tension was much more closely correlated to functional class than was lowered arterial oxygen saturation

tient at the time of surgery, the more likely he was to experience reduction in functional capacity later. This was especially true of the group over 60 years of age at the time of surgery. There were no striking differences between the functional capacities of the right and left pneumonectomy groups. In some patients, there was a correlation between the functional capacity and the abnormalities found on ventilatory function studies. In other patients, the functional limitation appeared to be based on a combination of decreased lung function and pulmonary hypertension due to increased pulmonary resistance [1, 20]

Pneumonectomy as well as extensive bilateral pulmonary resection results in a marked re-

duction of the total pulmonary capillary bed. Normally, only a portion of the total capillary bed of the lung functions at any one time. During exercise with an increase in the amount of oxygen uptake in the lungs associated with increased cardiac output, undoubtedly a greater fraction of the total lung capillary bed functions, as indicated by the lack of alteration in right heart pressure and arterial oxygen saturation in a normal individual.[22] In the patient who has undergone pneumonectomy, the blood flow through the remaining lung is doubled. If the total capillary bed of the remaining lung does not change and the functional capillary increases, then the reserve or nonfunctioning capillary bed of that lung is decreased. Consequently, when the oxygen requirements of the body are increased, such as by exercise, and the pulmonary blood flow increases, the reserve capillary bed may no longer be adequate to accommodate these demands. This would then result in an elevation in right heart pressure and possibly a concomitant fall in arterial oxygen saturation (FIG. 8).

Conclusions from these studies were as follows: (1) The older the patient at the time of pneumonectomy, the greater the possibility of a reduced functional capacity later. (2) Comparison of the functional capacity with the pulmonary artery pressures at rest and during moderate exercise suggests a direct relationship. As the functional incapacity increased, the levels of pulmonary artery pressure at rest and during exercise were found more elevated. (3) Reduction in functional capacity appeared to be more closely related to the effects of pulmonary hypertension than alterations in arterial oxygen saturation. (4) Pulmonary artery pressure-pulmonary blood flow relationships in the remaining lung after pneumonectomy differ from that of a normal lung and suggest a limitation in the expansibility of the vascular bed.

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Section VIII

OBSTRUCTIVE DISEASES OF THE CHEST

Bronchial Obstruction, Bronchitis and Bronchiolitis

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Introduction

THE primary functions of the tracheobronchial tree are the conduction of the air between the larynx and the pulmonary alveoli and the drainage of the lungs and the tracheobronchial tree itself. In the first function, the force for producing the air flow is the movement of the chest wall and the diaphragm acting through the intrapleural pressure The pressure is transmitted to the pulmonary alveoli and mediastinum, as well as to the soft tissues comprising the lung, bronchi and lower trachea The conduction must also contribute to the proper distribution of the air to every part of the lung, a function which is not fully understood at this time The efficiency of distribution of air almost defies description as it is impossible for the engineer to construct a system of tubes which will conduct air as efficiently as does the tracheobronchial tree If unequal distribution of the air occurs, exhaled air from one portion of the lung may be inhaled into another portion. Disturbance in time relationships has been observed by the author in localized obstructions due to foreign bodies and demonstrated in obstructive emphysema by the technic of fluoroscopic densiography[1] (Fig 1) For discussion of abnormal distribution, see Chapter 38

The second primary function of the tracheobronchial tree is drainage, not only of the lung, but of itself as well This function is as vital to life as the conduction of air. Interruption of this function produces death just as surely as does the interruption of air conduction, the only difference being that the time required is longer and the opportunity for the application of physiologically directed therapy is greater.

Many secondary functions may be ascribed to the tracheobronchial tree, and it is these secondary functions that contribute to and make possible the primary functions. The movements of the tracheobronchial tree may be classified as constriction and dilatation, lengthening and shortening, angular deviation and, finally, transmitted movements. On inspiration, the trachea and bronchi dilate, on expiration, they constrict. On inspiration, the bronchi lengthen, and on expiration they become shorter This is required, of course, by the movements of the lung, caused by expansion of the chest and the downward movement of the diaphragm When an elastic tube is lengthened, its lumen becomes smaller, and when it shortens, the lumen becomes greater This action is just the opposite to that which occurs in the bronchi, and it emphasizes the important role of the bronchial musculature and the elastic supporting structure for the lung and tracheobronchial tree. On inspiration, the bronchi deviate in an inferior and anterior direction—this produced by the descent of the diaphragm and the anterior and superior lifting of the anterior portions of the ribs and sternum Transmitted movements of the bronchi are produced by the pulsations of the heart and the great vessels

The second group of secondary functions may be termed the air-conditioning of the tracheobronchial tree This air-conditioning refers to the cleansing of the air by the deposit of particles of solid matter on the walls of the mucosa, to the warming of the air as it passes over the warm surfaces and, finally, the humidification of the air as it passes over the moist mucosal surfaces. The major part of this conditioning in the normal individual is accomplished by the nose. However, in the dyspneic patient, or

in the mouth breather, much of this air-conditioning function must be taken over by the trachea and bronchi.

The third group of secondary functions has to do with drainage of the tracheobronchial tree. The tracheobronchial mucosa is lined by a ciliated epithelium, the beat of the cilia occurring in the upward direction. Normal secretions of the lungs and tracheobronchial tree are handled completely by the ciliary action, so that *the mechanism of cough is not required* The ciliated epithelium extends up to the level of the vocal cords, and, at this point, the epithelium changes to a stratified squamous cell type The ciliated epithelium again occurs above the level of the vocal cords. The mucus may be drawn across the vocal cords by its own cohesive and elastic characteristics. When this is insufficient, it is necessary for the patient to clear the throat in order to carry the secretions over the unciliated area. It is for this reason that one of the first manifestations of increased bronchial secretion is clearing the throat. The presence or absence of a peristaltic action of the finer bronchi has been a debatable question for many years. Evidence at the present time, as developed by Di Rienzo, is strongly suggestive that at times a true peristaltic or milking action of the bronchi occurs which helps *to expel the secretion.*[4]

Cough is the mechanism for expelling bronchial secretions when the secretions are inadequately evacuated by the ciliary action. A thorough understanding of the mechanism of *cough is essential for the management* of excessive and retained secretions within the tracheobronchial tree. The cough cannot be considered as just a blast, for the action continues throughout the respiratory cycle. The first phase is an inspiration, secretions lying on the walls of the bronchi may be carried peripherally. The second phase—the tussive squeeze—is the contraction of the muscles of expiration with the larynx closed, producing a squeezing action on the alveoli, the bronchioles and the tiny bronchi, which move the secretion toward the mouth The third phase—the bechic blast—is the release of the closed larynx and the blast of air. The high speed of the air movement produced by the sudden release of the glottis carries the secretions in an upward direction. We must recognize that the cough may produce a to-and-fro motion of the secretion When the movement toward the mouth is greater, the cough is effective. One cough may not clear the bronchial tree, and it may have to be repeated; but when the downward movement is as much as the upward movement of the secretions, the cough is ineffectual. It is for this reason that a patient may cough but still not have effective bronchial drainage. The effectiveness of aspiration of the tracheobron-

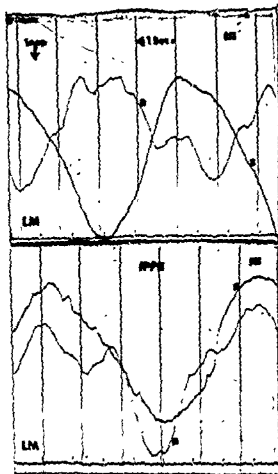


FIG 1—Fluroscopic densiogram, spirogram and electrocardiogram Male, 57 years. Obstructive pulmonary emphysema. Area left middle lung. Quiet breathing "D" densiogram recording variation in fluoroscopic density due to respiration over an area $\frac{5}{32}$ inch in diameter "S" spirogram Upper recording shows a reversal of air flow in the area as compared to airflow at the mouth Lower recording shows normal time relationship after a 20 minute IPPB-I treatment at 20 cm water pressure with 0 5 cc isoproterenol hydrochloride

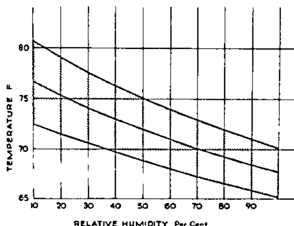


FIG 2—Comfort Chart Temperature and relative humidities for winter comfort in still air (15 to 25 feet per minute air movement) for 85 per cent of subjects (data from A S H V E Comfort Chart for Still Air)

chial tree, whether it occurs with bronchoscopy or by catheter, revolves around this phenomena of the to-and-fro motion of the secretion produced by coughing. The bronchoconstriction which occurs on coughing is greater than the constriction associated with a normal exhalation. This narrowing of the bronchi creates a high airflow rate and contributes to the effectiveness of the cough in expelling secretions

Physiologic Basis of Therapeutic Procedures

Regimen of Bronchial Hygiene

The following procedures are designed to create the most healthful conditions for recovery from diseases of the respiratory system and to correct the harmful environment our civilization has produced.

Elimination of dust The deposit of particles of dust and dirt on the moist mucosal surfaces of the tracheobronchial tree is irritating, and this is the case, whether or not the patient is allergic to the dust Ordinary cleanliness in the home, office and factory should be maintained. The use of vacuum cleaners rather than brooms and brushes, prevents the stirring up of dust Periodic cleaning of rugs and draperies eliminates a common source of dust. At work or at home in a dusty atmosphere, adequate ventilation, hoods, or even masks are utilized, but avoidance is the best procedure.

Elimination of smoke. Sources of smoke and fumes such as furnaces, heaters and chimneys should be carefully checked for proper operation. A patient who lives in a smoky atmosphere should be advised to move to a cleaner atmosphere.

Temperature. The healthful temperature is 68 to 72 degrees. This may be less than desired by many individuals, but with adequate humidity, as discussed below, the temperature is generally comfortable. The concept of the necessity for opening windows at night for healthful conditions is to be deplored. During the winter months, the cold air entering through the window, although its relative humidity may be high, is warmed by the air in the home and its relative humidity drops. Breathing the cooler air places an additional load on the warming mechanism of the body for the preparation of the air for the lungs, and so a greater load is placed on the tracheobronchial tree and particularly if the nose is inadequate. There is usually sufficient ventilation around doors and windows for replacement of oxygen and removal of carbon dioxide, so that opening of windows more than one-quarter inch is not necessary

Humidity Normal humidity is 40 to 50 per cent, and sometimes as high as 60 per cent. At this level, the load placed on the nose and tracheobronchial tree in the humidification of the air is not great At lower humidities, an additional load is placed on the tracheobronchial tree, and this load is not conducive to healing processes in the bronchi Humidities of 40 to 50 per cent will make temperatures of 68 to 72 degrees comfortable.

Air conditioning. Proper air conditioning is a valuable adjunct to the management of respiratory disease. It entails cleansing of the air of dust, smoke, fumes and odors, as well as control of air temperature, humidity and airflow. The sensation of comfort is related to the combination of temperature, humidity and airflow (FIG. 2) Proper hot weather air conditioning produces a drop in temperature of about 10 or 15 F. at the maximum, with normal relative humidity and an airflow of less than 25 feet per minute. If the changes are greater than these, the air-conditioning is uncomfortable, and may do more harm than good to susceptible individuals.

Upper respiratory infection. The management of upper respiratory infections in patients with recurrent or chronic bronchitis is extremely important. An upper respiratory infection may precipitate a recurrence of the bronchitis of which control has been obtained. Unless there are indications to the contrary, patients should be instructed to take an antihistaminic drug upon the first symptom of a cold, and in this way the more disturbing manifestations may be avoided. Bedrest is of prime importance in the control of upper respiratory infection, and in reduction of the incidence of complications. Although antibiotic therapy has little effect on the upper respiratory infection itself because of its viral nature, it does reduce the severity of secondary infection and the incidence of complications, especially when administered during the latter stages of the infection.

Relief of Obstruction

Sedatives and narcotics. The relief of apprehension and nervousness has an important role in the treatment of conditions being discussed. However, in the presence of respiratory obstruction, sedatives and narcotics may have a deleterious effect and, under some conditions, may be dangerous. Sedatives and narcotics, in addition to quieting a patient, may reduce his ability to fight for air. On the other hand, the quieting effect reduces the metabolic rate and reduces the ventilation and, therefore, the effort required to maintain an adequate ventilation. These drugs may also reduce the cough reflex, and thereby reduce the drainage of the tracheobronchial tree. This, of course, may lead to the retention of bronchial secretions, increase the respiratory obstruction and have an adverse effect on the patient. As a general rule, these drugs should be avoided in the presence of respiratory obstruction and the retention of bronchial secretions. It is essential to recognize that this is only a general rule, and exceptions are frequently encountered. The relief of pain, for example, may improve a patient's ability to cough.

Sedatives, and particularly narcotics, magnify the depression of the ventilation which occurs during the administration of oxygen in the treatment of chronic hypoxemic states due to respiratory obstruction. It is indeed unusual to encounter respiratory acidosis as a result of oxygen therapy in which narcotics have not been used. Nalline is an extremely valuable drug because it counteracts the depressant effect of the narcotics.

Excessive cough is frequently an ineffectual cough and may be greater than is required for the expulsion of bronchial secretions. Under these circumstances, the cough has not only a fatiguing effect on the patient, but it also irritates the bronchial mucosa and predisposes to advancement of the pathologic process. The use of sedatives, narcotics and various cough medicines can be a valuable therapeutic procedure. It must be borne in mind constantly, however, that the suppression of the cough is done for the purpose of reducing excessive coughing but not to reduce or stop effective coughing. It is thought that codeine decreases the amount of coughing with the minimum depression of respiration. There is controversy about the relative depressant effects of meperidine and morphine. Some investigators have developed evidence which indicates that meperidine has less of a depressant effect on respiration than does morphine, but the validity of their conclusions is questioned.

Oxygen. The breathing of concentrations of oxygen above that of air in the treatment of respiratory obstruction is of limited value. The use of oxygen does not improve the elimination of carbon dioxide, and may reduce the minute volume of ventilation. This predisposes to the development of respiratory acidosis, if the alkali shift is inadequate. This condition is most commonly encountered in the treatment of the chronic hypoxemic states on the basis of respiratory obstruction or interference with cardiopulmonary function. The administration of oxygen is beneficial in relieving hypoxemia occurring in the more severe types of obstruction. Oxygen must always be humidified for breathing, because it is very dry as it comes from the cylinder or pipeline.

Controlled oxygen therapy. The term *controlled oxygen therapy* is used to designate oxygen therapy in which the concentration of gas in the inhaled air is known and controlled. Such controlled therapy may be produced by the use

of the nasal or oral-nasal catheter and by the use of a diluting device with a reservoir type oxygen mask. A technic is described by Barach to maintain an oxygen flow of 1 L. per minute through the nasal or nasopharyngeal catheter for 24 hours, and then increasing it to 2 L. per minute for the next 24 hours, and so on, until a maximum of 6 to 8 L. of oxygen per minute is reached. The therapy may be discontinued by reversing the process. The disadvantage in the use of the diluting devices for the reservoir type of oxygen mask is that the diluting devices usually do not produce concentrations below 40 per cent, and this concentration may be sufficiently high to produce respiratory depression and the resulting respiratory acidosis if the alkali shift is inadequate. The partial rebreathing types of oxygen masks are contraindicated for the treatment of such cases, because of high carbon dioxide concentrations in the inhaled gas with low oxygen flow rates. The present day oxygen tents are inadequate for this type of oxygen therapy and are considered to be definitely contraindicated.

Helium-oxygen. Helium has an atomic weight of 4.003, as compared to nitrogen with an atomic weight of 14.008. The density of helium with 21 per cent oxygen is less than the density of air. Under equal pressures, a larger volume of helium and oxygen will flow through an orifice than will air. An increase in the minute volume of inhalation frequently results when the helium is substituted for the nitrogen. The diffusion of a gas with a lower density is faster than that of a gas with higher density. This increase in the diffusion rate may speed the exchange between the alveolar air and the tidal air and contributes to the benefit derived from this therapy.

However, helium has a higher viscosity than nitrogen, so more force is required for flow through an obstruction whose length is much greater than its diameter. This probably accounts for the failure of helium-oxygen to benefit some cases. The gas for medical purposes should always be obtained with at least 20 or 21 per cent oxygen. Higher oxygen concentration may be obtained or may be produced by mixing with pure oxygen from an additional supply. The most practical method of administration is by a tight-fitting mask of the reservoir type. Administration by catheter or oxygen tent is generally ineffectual.

Bronchodilator Drugs

Epinephrine. The subcutaneous or intramuscular administration of epinephrine relaxes spasm of the bronchi and may be of value in certain of these cases. The administration of this drug is a valuable diagnostic procedure as a means of evaluating increased bronchial spasm. It is applicable in the evaluation of cases of bronchiolitis. Doses of 0.2 cc. to 0.4 cc. are within the desired range for adults. When used therapeutically, refractoriness may develop and progressively larger doses become necessary, which is to be avoided.

Aminophylline. Lessening of the dyspnea of bronchial obstruction may be accomplished by the administration of aminophylline. The action is attributed to the relief of bronchospasm as well as improving pulmonary circulation. Intravenous administration, preferably by intravenous drip, is thought to be most effective. Rectal suppositories are frequently effective. Various oral preparations of aminophylline are available in which combinations with other drugs are made in order to avoid the gastric irritation from the oral administration.

Ephedrine. Although the action of ephedrine in the relief of bronchospasm is not as effective as that of epinephrine, it does appear to have a beneficial effect in the treatment of bronchiolitis. It is sometimes effective in other bronchospastic diseases.

Bronchodilator aerosol. The aerosol administration of epinephrine, racemic epinephrine and isoprotenol is effective in the relief of increased bronchial tonicity. The vasoconstrictor effect of these drugs may reduce the vasodilatation of the bronchial mucosa and contribute to part of the beneficial effect. The particle of the aerosol must be extremely small, with an average diameter of about 3 microns or smaller. The small diameter is required in order for the drug to stay in suspension and reach the deeper portions of the tracheobronchial tree. Larger particles, if not removed within the administrative device, will be deposited on the mouth, pharynx, larynx, trachea and larger bronchi, and the

effectiveness will be greatly reduced. The aerosol administration of these drugs may be useful when there is refractiveness to other means of administration. The usual concentration of the drug in solution is generally 1:100 or 1:200, as compared to the usual dilution of 1:1000 for systemic administration.

Vasoconstrictor aerosol The inhalation of a vasoconstrictor aerosol such as Neo-synephrine, either alone or with a bronchodilator aerosol, is beneficial in some cases, particularly when there is bronchial mucosal congestion.

Intermittent positive pressure breathing. Intermittent positive pressure breathing apparently improves the distribution of air to the various parts of the lung and may produce aeration of portions of the lung not being ventilated prior to the treatment. It also has a beneficial effect in pulmonary edema. This procedure is enhanced with the administration of a bronchodilator drug by aerosol. It is thought by some, that this action is the principal value of the intermittent positive pressure breathing. (See Chapter 55 for further discussion of IPPB and aerosol administration)

Bronchoscopy. In addition to the diagnostic information to be derived from bronchoscopy, certain therapeutic procedures may be applied which will be helpful in relieving obstruction in the major and lobar bronchi and in the segmental bronchi which are accessible to the bronchoscope Dilatation of narrowed areas of the bronchi by means of dilating forceps, or by actually passing the bronchoscope through the area, may be of some value The removal of granulation tissue and neoplastic tissue, using forceps of varying types, will relieve bronchial obstruction. Tumors in the lower trachea and in the main bronchi sometimes can be completely or partially removed by the coring procedure, i e., forcing the bronchoscope through the neoplastic tissue, and thereby dislodging fragments which may be removed by aspiration, with forceps, or removed through the bronchoscope Electrocoagulation procedures may sometimes be applicable to neoplastic processes.

Tracheotomy Tracheotomy as a means of relieving respiratory obstruction is applicable to the obstructions above the level of the upper trachea. Obstructions in the middle and lower portions of the trachea sometimes may be relieved by tracheotomy through the use of extra long tracheotomy tubes, wide curved tracheotomy tubes and cane-shaped or flexible tracheotomy tubes. The use of these tubes over a period of time is generally unsatisfactory because of necrosis of the trachea, which may occur from pressure and the procedure of changing the tracheotomy tube. Tracheotomy as a means of relieving obstruction at the carina or the main bronchi is usually of little value. The use of tracheotomy as a means of relieving the retention of bronchial secretions is discussed later in this chapter.

Relief of Retention of Bronchial Secretions

Water balance. Water is the substance which makes the bronchial secretions liquid, and an adequate water balance is extremely important for the production of fluid bronchial secretions. Water, therefore, is a true expectorant. However, in the presence of respiratory obstruction, the administration of intravenous fluids must be done with caution, and particularly so if inspiratory obstruction is present. Hypoxemia and a high negative inspiratory pressure predispose to the development of pulmonary edema If fluids are given in too large amounts or administered too rapidly by the intravenous route, pulmonary edema may occur.

Expectorants. In the presence of an adequate water balance, expectorant drugs produce a diluting or thinning action on the bronchial secretions. Potassium iodide is considered the most satisfactory of all the expectorants The effectiveness of ammonium chloride as an expectorant is questioned. The ammonium chloride is irritating to the gastric mucosa, and it is thought that this irritation—by reflex action—produces an increased flow of bronchial secretions which assists liquefaction of the bronchial exudates.

Humidity therapy. As mentioned previously, the nose, pharynx and larynx warm and humidify the incoming air in preparation for the lungs. In dyspneic states there is usually mouth breathing and th[illegible]

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tracheobronchial tree. This results in a continuous evaporation of moisture from the surfaces of the trachea and bronchi. The breathing of air with an increased amount of water in it replaces this function of the upper air passages and reduces the evaporative loss from the tracheobronchial tree. This reduction in the evaporative loss allows the moisture to remain in the bronchial secretions, and they become less viscid. When saturated air at about 70 F. is raised to body temperature, the relative humidity is reduced from 100 per cent to approximately 50 per cent, and for this reason the breathing of air with a 100 per cent relative humidity has little direct effect on the bronchial secretions. It is the reduction in the evaporative loss from the bronchial secretions which is the actual mechanism of liquefaction.

Humidity therapy may be considered as normal humidity, high humidity and water-aerosol therapy. Normal humidity is considered to be from 40 to 50 or even 60 per cent relative humidity. This is the best humidity for healthful conditions in living and working areas. This humidity reduces the incidence of respiratory infections and speeds recovery from the common cold.

High humidity varies from 90 to 100 per cent, and its effectiveness is greatest when the humidity is at its highest. It is most useful in the treatment of conditions in which there is retention of bronchial secretion. The use of heat as a means of evaporating water to increase the humidity is unsatisfactory because of the rise in temperature produced in the patient's environment. The mechanical humidifier which breaks the water into tiny particles and blows them out into the air is the apparatus of choice. Such a humidifier may be placed in a small room, from which the drapes have been removed in order to reduce the absorption of water. The ventilation in the room should be reduced to a minimum. The effectiveness of this therapy may be increased by placing the patient within an enclosure such as the canopy of an oxygen tent or the modern type of croup tent. This is to be differentiated from the old-fashioned croup tent in which heat is used to evaporate the water.

Water aerosol. Water aerosol therapy is essentially of the production of water fog for breathing. This fog may be produced by the mechanical type of humidifier previously mentioned. For this therapy it is essential that the particles of water be of small size, i.e., a true aerosol. These small particles of water evaporate into the air as it is warmed during the process of inhalation, and further reduce the evaporative loss from the bronchial secretions. When a generous fog is used, the particles which do not evaporate are deposited to a considerable extent on the bronchial secretions and contribute in that fashion to their liquefaction. Aerosol generators may be used to produce the water fog for direct application to the patient. This application may be made by attaching the outlet of the aerosol generator to a face mask or a face tent. Compressed air or oxygen is the most common source of energy used for the operation of the aerosol generators.

Heated aerosols administered by the technics of Miller[3] or Barach[2] appear in some cases to be more effective than the unheated. The evaporation of the aerosol into the inhaled air at the higher temperature reduces the amount of water evaporated from the mucosal secretions thus permitting more effective liquefaction of the thick secretions.

Oxygen therapy may be combined with high humidity and aerosol therapy. In oxygen tent therapy, the water aerosol may be delivered to the circulating gas in the oxygen tent, a large amount of water aerosol is required because the cooling coil in the refrigeration unit precipitates the moisture by its low temperature. Oxygen tents are available which are designed to produce high humidity and fog therapy. High humidity therapy with an oxygen mask may be obtained by passing the oxygen through an effective humidifier such as the type commonly used with nasal oxygen catheters. It should be borne in mind that oxygen masks of the reservoir type supply the oxygen practically dry unless procedures are used to supply additional water to the oxygen. The administration of nasal oxygen in the presence of water fog or high humidity is a satisfactory means of combining the two methods of treatment.

Wetting agents. A wetting agent added to the water placed in the aerosol generator reduces

the surface tension of the droplets deposited on the bronchial secretions so that the water penetrates the secretion more readily and more rapidly, and this enhances the liquefaction action

Aspiration of secretions. Aspiration of secretions from the tracheobronchial tree may be a life-saving procedure in patients with retention of bronchial secretions. The catheter for aspiration may be passed through the nose and guided blindly into the larynx, or guided by the use of the finger, or by observation with the laryngeal mirror. The catheter may be passed through the mouth and a stylus used to direct it between the vocal cords. An intratracheal tube may be used as a means of passing the catheter into the tracheobronchial tree.

Bronchoscopy furnishes a more effective means of aspiration of the tracheobronchial tree than does the catheter. The direct observation and the passage of the aspirator into the various parts of the tracheobronchial tree accounts for its more effective action. The use of the flexible curved and straight aspirators enables the aspirator to conform to the direction of the individual bronchus being aspirated. Active cough reflex is essential for the greatest response to aspiration, whether it be by catheter or by bronchoscope If the cough reflex is not active, then the secretions are removed only from the actual area at the end of the aspirator. The observation of a single "plug" of secretion at bronchoscopy is unusual. Rather than a plug, the bronchus is completely filled by the secretion. The neighboring bronchi are usually covered by a layer of secretion, with the air passing through the tunnel created by the secretions. Local anesthesia for these procedures must be used with caution to prevent the suppression of cough during the procedure. The spraying of the throat with an anesthetic solution is frequently used, but the instillation of the anesthetic solution into the main bronchi may reduce the cough reflex so that an adequate aspiration is not achieved. A good strong aspirating machine is essential in order to remove quickly the secretion as it is coughed up to the end of the aspirator.

Tracheotomy. During recent years the use of the tracheotomy as a means of improving drainage of the tracheobronchial tree has received more and more emphasis The advantage of this procedure is that a catheter may be passed easily and as frequently as it is required for the removal of the secretions. In the seriously ill patient, it has been observed that the procedure of tracheotomy done at the bedside is easier on the patient and more beneficial than the repeated passage of a catheter or bronchoscope. It is especially useful in the treatment of postoperative bronchopulmonary complications. Tracheotomy, as a prophylactic procedure at the time of surgery, may be employed in extensive thoracic surgery, such as esophageal resection.

Because the air-conditioning action of the nose is lost by a tracheotomy, high humidity and water aerosol therapy are indicated. In adults, the latter is best achieved by an aerosol generator and tracheotomy mask A wetting agent in the aerosol is effective if the secretions are inadequately liquified. The need for humidity (therapy) increases inversely to the age of the patient.

Inspiratory positive pressure with high velocity exsufflation (Barach). The inflation of the chest by positive pressure up to 40 cm., with practically instantaneous reversal to 40 cm of negative pressure, is useful in promoting bronchial drainage. The rate of air movement during the expiratory phase approaches the rate of air movement during a normal cough. In the patient with retention of bronchial secretion, the rate of air movement produced by the "cough machine" may exceed the rate of air movement that the patient is able to produce by coughing. This apparatus may have its greatest field of usefulness in cases of respiratory paralysis, but it also may be effective in the treatment of conditions characterized by the retention of bronchial secretions This apparatus promotes bronchial drainage even when the natural cough is ineffectual It is especially useful following bronchoscopic aspiration, and in the treatment of postoperative bronchopulmonary complications. It is essential that the apparatus produce the full 40 cm. of water pressure, both on expiration and inspiration.

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situation is conducive for the development of lung abscess or, in the cases of longer duration, bronchiectasis. The severe inflammation produced by the retention of secretion results in the destruction of the epithelium, some of the musculature and some of the elastic tissue, resulting in a loss of tone of the bronchial wall and the dilatation These dilatations are generally of the saccular type rather than of the cylindrical type If the condition persists for a sufficient length of time, the bronchiectasis occurs even though the obstruction may subside and the lung becomes aerated again

Evaluation of Respiratory Obstruction

Evaluation of changes in the degree of generalized respiratory obstruction during acute illness may be accomplished by careful clinical observation of the patient. No one sign may be considered alone, but the observations must include all signs and symptoms, although one or more particular signs may have to be emphasized in the evaluation The heart rate and respiratory rate are valuable measurements, but they must be considered in terms of the activity of the patient, e g , the rates measured when a child is struggling in bed as compared to the rate while asleep may not be a valid comparison When the heart rate is slower (when the child is sleeping) it does not necessarily indicate improvement or lessening of the obstruction Observation of the retractions of the different parts of the body may be of great value It should be borne in mind that retractions as a rule are greater in infants than older children, and greater in children than in adults. The retractions in the neck and upper chest are generally greater in the presence of laryngeal or high tracheal obstruction than they are in bronchial or low bronchial obstructions. For the purpose of this evaluation, the neck, chest and abdomen may be divided into areas: the midline, adjacent to the midline, the suprasternal area, then the sternal area and, finally, the epigastrium, on each side there is the supraclavicular area, the infraclavicular area and the

... The notation of the presence or absence of retraction in each of these areas, and compared at a later time with the retractions in the same areas, may give significant information. The observation of activity of the accessory muscles of inspiration gives valuable information, but it must be recognized that this information is mostly of value in observing whether or not the accessory muscles are used. Inspection of the patient as a whole may give evidence of the degree of exhaustion The estimate of exhaustion must be correlated with observation of the other findings; e.g , there may be a decrease in the amount of retraction and an increase in the exhaustion. This may indicate that the obstruction is progressing, or the patient's ability to breathe is deteriorating because the exhaustion is progressing, and the patient is no longer able to make as great a respiratory effort.

The terms respiratory embarrassment and respiratory decompensation are useful terms for discussing the phenomenon of respiratory obstruction. The term respiratory embarrassment indicates that the patient is making an abnormally great respiratory effort, but that the primary functions of supplying oxygen and eliminating carbon dioxide are within reasonably good physiologic limits. The term respiratory decompensation indicates that the primary function is inadequate When this occurs, the patient's course is a fatal one unless intervention of management is successful When the exchange of oxygen and carbon dioxide is inadequate, it reduces the patient's ability to use his muscles to the greatest advantage in maintaining the air movement, so that a vicious cycle is established The greater the decompensation, the less efficient are the muscles, the condition increases the degree of respiratory decompensation The change from respiratory embarrassment to respiratory decompensation is usually a matter of clinical interpretation. Theoretically, decompensation occurs when a significant degree of hypoxemia develops.

Bronchitis

The physiologic effects of bronchitis are related to the swelling of the mucosa, the type and amount of secretion, the adequacy of drainage, the response of the bronchial musculature

Bronchial Obstruction

This discussion of bronchial obstruction will be limited to that of the major and medium-sized bronchi It is not intended to discuss the bronchial obstruction associated with diseases such as bronchial asthma and diffuse obstructive pulmonary emphysema, although the same principles apply to bronchial obstruction regardless of its cause and location

Many classifications of bronchial obstruction have been suggested, but the classification which follows is one which presents the information required for our discussion in this chapter

- I Pathologic
  - a. intramural
    - 1. endogenous: secretion, broncholiths
    - 2 exogenous foreign body
  - b mural inflammation, edema, neoplasm
  - c. extramural pressure
- II Functional
  - a minimal wheeze
  - b partial expiratory (emphysema)
  - c. complete atelectasis

The first clinical sign of bronchial obstruction is the wheeze, a phenomenon caused by the increased speed of air movement through the narrowed area of the bronchus with turbulence in the airstream The first alteration demonstrated by pulmonary function study is a slowing of the speed of expiratory air movement because of bronchial narrowing during expiration As the obstruction progresses, the wheeze increases in intensity and complete obstruction, during expiration, occurs It is not a complete obstruction *to inspiration* because of the bronchial dilation during inspiration, and because inspiration is more forceful than expiration. This produces the classic picture of emphysema Chest x-ray taken on inspiration reveals normal findings. The chest x-ray taken on expiration reveals the lung on the involved side still to contain practically the same amount of air. The diaphragm is depressed, the mediastinum is *displaced away* from the obstructed side, and the spaces between the ribs remain wide as they were on the inspiratory film As the obstruction increases, *it tends to occur during inspiration and expiration*, and the classic picture of atelectasis is noted. On both the inspiration and expiration chest x-ray film, the involved area of the lung has a greater than normal density, the mediastinum is displaced toward the involved side, the diaphragm is elevated and the interspaces between the ribs are narrowed.

Interference with the drainage of the tracheobronchial tree occurs in bronchial obstruction and is just as important as the interference with air conduction. In the case of minimal obstructions, e g , localized inflammation or early neoplastic disease, the ciliary action may be lost in the region of the obstruction If this area is great enough, the secretions may not be drawn across the inactive cilia, so that the cough must take over the expulsion of the secretions In the area of slight bronchial obstruction, the air speed through the area is increased because of the reduced cross sectional area of the lumen. This increased air speed may be traumatic to the delicate epithelium, and reduce or stop ciliary action, cough must again take over the passage of the secretions through this area As the obstruction increases, interference with the bronchial drainage also increases, and generally the cough increases. *If the cough* is inadequate in expelling the secretions, the retention of the secretions itself stimulates the formation of more secretions and more inflammation, and establishes the vicious cycle. If a bronchitis were present prior to the occurrence of the bronchial obstruction—either acute, subacute or chronic—the interference with bronchial drainage is a serious phenomenon This retention of secretion, in itself, may produce greater inflammatory changes in the area of the obstruction and increase the obstruction. The retention of the bronchial secretions within the obstructed area of the bronchial tree supplies a rich media for the growth of organisms already present and for the growth of pathogenic organisms The retention of the bronchial secretions may produce the drowned lung, in which the bronchi and the alveoli become filled with the retained secretion. *Usually*, fever *and an* elevated white count are evidence of the infection, however, these signs may be masked by antibiotic therapy. In this condition, the

The pathologic changes in the bronchial mucosa consist of changes varying from thickening to thinning, but generally are characterized by some degree of obstruction. The thickening of the mucosa may be the result of vasodilatation and congestion or edema, or may also be the result of hypertrophic changes In the severe forms of long duration, usually of the infectious type and associated with bronchiectasis, atrophic changes may be present Infiltration of the mucosa by round cells or leukocytes, or both, is characteristic of the changes in chronic bronchitis If these changes involve the smaller bronchi and extend into the bronchioles, the pathologic process usually extends into the alveolar septa.

The first effect of the narrowing of the bronchi due to chronic bronchitis is the slowing of the air-flow rate on expiration. This effect may be demonstrated by means of the vital capacity recorded on a high-speed drum or by means of the pneumotachograph This narrowing of the lumen has its greatest effect on the higher rates of air flow and is, accordingly, most easily measured by noting the alteration in the maximum speed of expiration The highest speed of air flow occurs at the beginning of inspiration and at the beginning of expiration. These speeds may be determined with a fair degree of accuracy by means of the Benedict-Roth type of spirometer with the drum moving at five times the normal speed or faster. In performing the vital capacity, it is essential that the importance of fast and forceful inspiration and expiration be stressed to the patient. The pneumotachograph is the much more satisfactory and precise instrument for measuring air-flow rates, but the spirometer gives adequate evaluations in clinical practice

As the bronchial obstruction increases, the maximal inspiratory flow rate (MIFR) may be reduced The reduction in the maximal expiratory flow rate (MEFR) is generally greater than the reduction in the MIFR. In younger individuals, 4.00 L. per second is usually the minimum normal speed. In the older age groups, the normal speeds may decrease to 3.00 L per second

The type of obstruction in chronic bronchitis is different from the type of obstruction that is generally seen in acute bronchitis. This difference is due to the fact that the mucosa in chronic bronchitis is usually thickened and somewhat rigid. In acute bronchitis, the swelling is softer and the mucosa is displaced in such a fashion that the obstruction is increased and becomes proportionately greater during the expiratory phase. In chronic bronchitis, if there is increase in the tonicity of the bronchial musculature, or if collapse of the bronchi is the predominant feature, such as might occur from loss of elasticity, the obstruction then becomes greater during the expiratory cycle, and a typical expiratory curve is produced. From this discussion it readily becomes apparent that we can differentiate two general types of bronchial obstruction. first, slowing of the maximum expiratory and inspiratory flow rates, and, second, progressive increase in the bronchial obstruction during the expiratory phase. The first type of bronchial obstruction is termed "organic" because it is the result of thickening and stiffness of the mucosa and is present throughout the respiratory cycle. The second type is termed "functional" bronchial obstruction because it is related to the respiratory cycle and to abnormal movements of the bronchi and the supporting structures of the bronchopulmonary architecture. These two types of bronchial obstruction may exist in the same patient, and the evaluation of the forced expiratory spirogram makes this apparent. In an occasional patient with a severe form of diffuse obstructive emphysema, the functional type of bronchial obstruction may not be apparent In some cases this is caused by a sudden great increase in the degree of bronchial obstruction due to collapse of the bronchi and the sudden stoppage of expiration. Following the inhalation of a bronchodilator aerosol, this sudden stoppage of the air flow may be reduced, and the vital capacity increases by allowing a greater exhalation. When this occurs, the expiratory curve becomes more marked, and it is apparent that there is a combined type of obstruction as shown by the presence of this expiratory curve as well as by the slowing of the maximal expiratory and inspiratory flow rates. This evaluation of air-flow rates permits an approach to the problem of determining the

and primary disease prior to the onset of the bronchitis

For the purpose of this discussion, bronchitis is divided into the following types: acute, subacute and chronic; asthmatic bronchitis and postoperative bronchitis Acute, subacute and chronic bronchitis will be considered together. The other types, being variations of these, will be discussed separately

Acute, Subacute and Chronic Bronchitis

Pathologic physiology of the bronchial mucosa. Acute bronchitis as a distinct clinical entity is exceedingly rare It is most often associated with a generalized upper respiratory infection —the common cold The upper respiratory infection may predominate in its effect on different parts of the respiratory tract, namely, the nose, pharynx, larynx, trachea or the bronchi.

Acute bronchitis is characterized by swelling and edema of the bronchial mucosa The mucosal surfaces are generally congested, and there frequently is loss of ciliary activity The mucous glands are distended, and may contain purulent material. In the more severe cases, desquamation of the mucosa is marked, along with the presence of adherent mucopurulent and purulent secretions The disease is generally self limited, and recovery is complete

Because of the narrowing of the lumen of the bronchi on expiration, the swelling of the bronchi in acute bronchitis has its greatest effect on the air flow during expiration, in the normal individual, this effect is so slight as to be hardly noticeable. If the patient undertakes relatively heavy exertion, he may notice shortness of breath, and, in the severe types, wheezing on expiration may occur. In patients with conditions existing prior to acute bronchitis which limit the normal bronchopulmonary functions—such as thickened mucosa, loss of elasticity of the bronchial walls, generalized bronchial obstruction, obstructive emphysema, bronchial asthma and pulmonary fibrosis—the swelling of the mucosa may produce very profound physiologic changes. The swelling of the mucosa and normal narrowing of the bronchial lumen on expiration produce a degree of expiratory bronchial obstruction which sustains the high positive intrapleural pressure during cough. This high pressure is transmitted throughout the chest in a fashion similar to the transmission of pressure by fluid. The pressure wave through the airways is slowed down by the bronchial obstruction, and this produces a greater than normal differential pressure—on coughing—between that on the bronchi from the outside and on the bronchi from the inside. The result of this is collapse of the bronchial wall. This collapse is generally more marked in the smaller bronchi than it is in the major bronchi The high pressure on the bronchial mucosa in the areas of obstruction is irritating to the mucosa and, undoubtedly, increases the degree of inflammation by the mechanical action of the pressure and the high rate of air flow through the narrowed areas. The obstruction reduces the speed of the expiratory blast and reduces the effectiveness of the cough These various factors contribute to and amplify each other

As the acute phase of the bronchitis disappears, the cough may continue, and the stage of a subacute bronchitis occurs This is characterized by the persistence of cough, which usually becomes less productive The patient frequently attributes the cough to a tickle which may be localized in the pharynx, larynx, trachea or upper chest, depending on the site of the greatest degree of inflammation. The cough is frequently spasmodic in nature, and when the cough does start, it continues for some time, until the patient brings it under control by suppressing the cough reflex. This phase of bronchitis is unusual in the normal individual but is more likely to occur in patients who have had the more severe forms of bronchitis and in those who have had a preceding chronic bronchitis, asthma, hayfever, sinus disease and/or nasopharyngitis

Chronic bronchitis, in the sense of a bronchitis of long duration, presents one of the most serious problems in treatment, and one of the frequently overlooked problems in the management of chronic pulmonary disease The type of inflammation that is catarrhal, allergic, or suppurative (as will be discussed later) produces the classic symptoms of persistent cough, with the type and amount of sputum related to the type and severity of the inflammation.

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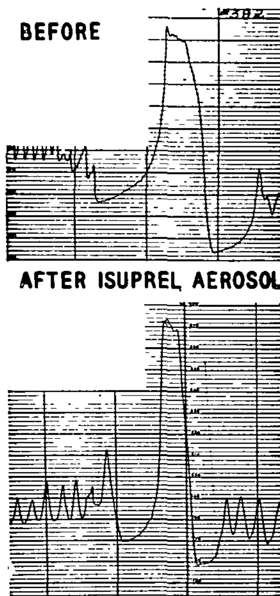


FIG 3—F R E No 392 Vital capacity Drum speed 16 cm per minute Diagnosis chronic diffuse obstructive pulmonary emphysema, arteriosclerotic heart disease and chronic catarrhal bronchitis Maximal inspiratory and expiratory flow rates 1 60 L per second and unchanged by bronchodilator aerosol Volume, trapping and expiratory curve improved Bronchoscopy revealed bronchial inflammation, and sec [illegible] confirmed the catarrhal [illegible] struction

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Pathologic physiology of bronchial secretion Bronchoscopy is of paramount importance in the evaluation of bronchial inflammation, with the exception of its contraindication in the presence of acute inflammation. However, in the presence of subacute or chronic inflammation, the information derived from the bronchoscopy is of great importance in the diagnostic approach and therapeutic procedures involved in the treatment. The bronchoscope permits study of the configuration of the bronchi and the appearance of the mucous membrane. An evaluation can be made of the

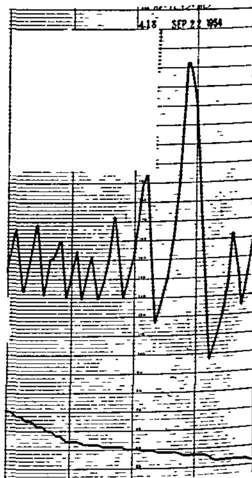


FIG 4—F R E No 418 Vital capacity. Drum speed 16 cm per minute Diagnosis pulmonary fibrosis and chronic suppurative bronchitis Maximal inspiratory and expiratory flow rate were 1 08 L per second, and expiratory curve was within normal limits Bronchoscopy revealed bronchial inflammation, retention of secretions, and sections of bronchial secretion confirmed the suppurative bronchitis. Previous therapy for emphysema had been ineffectual Repeated bronchoscopic aspirations, autogenous vaccine and oral aerosol antibiotic therapy resulted in marked improvement and return to full-time employment These findings indicate an organic type of bronchial obstruction.

appearance, amount and origin of the secretion. The appearance of the secretion is not always a reliable index of its type, and histologic examination is an extremely valuable procedure. The secretion is centrifuged and the sediment mounted in a paraffin block, sectioned and stained in the conventional way. The microscopic observation of the secretions gives an index to the character of the secretion and, therefore, to the pathologic process producing the secretion, which is much more accurate than the mere inspection of the secretion or the examination of smears. The presence of pure mucus is indicative of hypersecretion rather than of an inflammatory or infectious process. The presence of mucus with desquamated bronchial lining cells, round cells and lymphocytes supports the diagnosis of a catarrhal type of bronchitis. The presence of eosinophils is suggestive of an allergic bronchitis.

During the early phase of acute bronchitis, there usually is no particular increase in the amount of bronchial secretions. Cough is frequently a predominant and troublesome symptom in this phase and is probably related to some retention of bronchial secretions. As the inflammatory process proceeds, the bronchial secretions become more plentiful, and an exudate is formed. The cough at this time becomes productive. The activity of the ciliated cells of the bronchial mucosa is generally limited, and bronchial drainage then relies on the cough mechanism. If the secretions are thick and viscid, retention may occur and contribute to bronchial obstruction. Under these circumstances the presence of the secretion lying on the walls of the bronchi makes the inflammatory process more severe. It is during this phase of the disease that the use of humidity is of considerable value in therapy.

Bacteriologic examination of the bronchial secretions is extremely important and may produce information of significance for management. This examination comprises smears, cultures, sensitivity tests and, when appropriate, guinea pig inoculation. In appropriate cases, these smears should include the potassium hydroxide preparation for the recognition of fungi as well as the Gram and acid fast stains. The cultures should entail the growth and identification of all organisms which appear. The practice of reporting only one organism as being the predominant organism is inadequate in the management of chronic bronchitis. The identification of fuso-spirillo-form organisms in bronchoscopically collected secretions obviates the possibility of oral origin and serves as an indication for specific chemotherapy such as iron cacodylate intravenously.

Pathologic physiology of the bronchial musculature. Obstruction occurring in acute bronchitis is the result of swelling of the mucosa, retention of the bronchial secretions and increase in tone and/or movements of the bronchial musculature. In the normal individual, it is probably unusual for the bronchial musculature to be affected by respiratory infection. It is well known that patients who have a seasonal type of bronchial asthma are much more likely to exhibit signs of bronchial obstruction during acute bronchitis than are patients who are completely normal.

Asthmatic bronchitis. Asthmatic bronchitis is considered an acute bronchitis with the findings of bronchial asthma consisting of dyspnea and expiratory wheezes. It is not logical to apply this term to the increase in symptoms in an asthmatic patient produced by acute bronchitis. The term is limited to the occurrence of asthmatic findings only during the period of acute bronchitis. As previously mentioned, the symptoms are brought on by the reaction of the bronchial musculature to the inflammatory process in combination with the swelling of the mucosa and the retention of bronchial secretions.

Treatment. The treatment of bronchitis is directed along the lines of the abnormal physiology. The regime of bronchial hygiene, humidity therapy, expectorants, relief of bronchial obstruction, assistance in the removal of bronchial secretions and control of cough are important (see Chapter 55).

The treatment of associated bronchitis in pulmonary disease is not infrequently of considerable benefit. Localized bronchial obstruction due to swelling, retained secretion and increased muscle tone may contribute to the pathologic process in the pneumonias, lung abscess and pneumonitis.

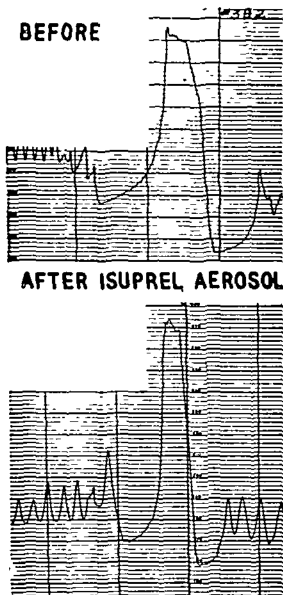


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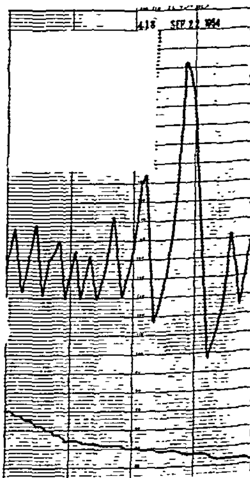
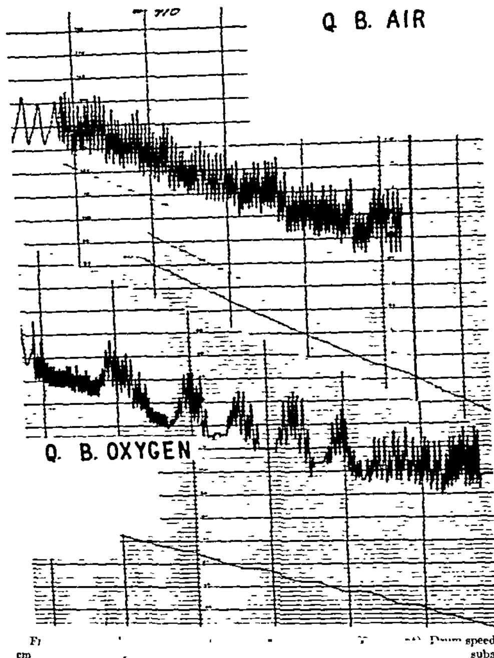


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Fi [illegible] Drum speed: 3 2 cm [illegible] subacute bronchitis Efficiency $\left(\frac{[illegible]}{\text{min } O_2 \text{ consumption}}\right)$ was [illegible] per cent [illegible] increased to 4 8 per cent breathing oxygen with marked rhythmic irregularity of the pattern These findings are indicative of chronic hypoxemia with primary respiratory control by oxygen tension, and of a predisposition to respiratory acidosis from uncontrolled oxygen therapy

predominant etiologic factor. Bronchoscopically, these patients show a variable degree of hyperemia of the tracheobronchial mucosa. The secretions are rather scanty, and it is necessary to irrigate the bronchi with normal saline in order to obtain an adequate specimen for examination. Bacteriologic examination is usually not remarkable. Histologic examination of the bronchial secretions generally reveals the presence of mucus and few cells. In the absence of other etiologic factors, a remarkable response is usually obtained in this type of patient when

Antibiotic therapy. Acute bronchitis is usually a self-limited disease, with complete recovery. However, antibiotics may speed the recovery, particularly in the stage characterized by the production of thick mucoid, mucopurulent or purulent secretion. The antibiotic aerosols in acute bronchitis are of questionable value, and the possibility of sensitizing the patient presents a hazard. The patient with a definite chronic suppurative bronchitis may not present the usual systemic manifestations of an infectious process, such as an elevated white count or fever. In spite of this, antibiotic therapy may be of distinct value The pathologic changes in the bronchial mucosa frequently reduce the blood supply to the bronchial mucosa and lessen the effectiveness of systematic antibiotic therapy Thus, aerosol administration in chronic bronchitis is of value Aerosol therapy is considered an adjunct to systemic therapy, rather than a substitute, although it has been shown that there is absorption of penicillin from the bronchi during aerosol therapy With the numerous antibiotics which are now available, the selection of the one most likely to succeed may present a problem The sensitivity tests performed on the bronchial secretions collected bronchoscopically and uncontaminated by secretions from the mouth and pharynx furnish a reasonable basis for the selection of the antibiotic If the response to the drug is inadequate, a change may always be made, and the sensitivity test disregarded in favor of clinical evaluation.

Oxygen therapy Patients with chronic dyspneic disease and a superimposed acute or subacute bronchitis frequently have an increase in dyspnea because of mucosal swelling, increased bronchial tone and retention of bronchial secretions Serious respiratory obstruction may occur, and presents a serious problem. Therapy includes the use of oxygen, but entails the danger of respiratory acidosis. In the presence of chronic hypoxemia, the control of respiration shifts from the central centers in the medulla oblongata to the peripheral centers along the carotid arteries. The peripheral centers are primarily sensitive to blood oxygen tension, as opposed to the central centers which are primarily sensitive to carbon dioxide tension. An increase in the blood oxygen tension reduces the minute volume of ventilation and increases the carbon dioxide tension. If the alkali shift is inadequate to buffer the increased carbon dioxide retention, respiratory acidosis follows. Respiratory depression produced by narcotics and sedatives predisposes to respiratory acidosis.

Comparison of respiratory tracings while breathing air and oxygen show a characteristic response. Efficiency of quiet breathing is an expression of the relationship between the minute volume of air inhaled and the minute volume of oxygen absorbed. Normal subjects and many patients with bronchial obstruction show an increase in the efficiency of quiet breathing between air and oxygen, but no change in the respiratory pattern. Patients with chronic hypoxemia and respiratory control primarily by oxygen tension may show, in addition to the increase in efficiency, an increase in the irregularity of quiet breathing (Fig 5)

Many of these patients exhibit an elevated respiratory rate If the rate decreases markedly with oxygen therapy, the possibility of an impending respiratory acidosis is considered The symptoms consist of temporary improvement in dyspnea followed by irritability, emotional disturbance, coma and death.

These patients are benefited by gradually increasing the oxygen concentration, this is an extremely valuable part of the therapeutic armamentarium Assisted respiration by means of a respirator or intermittent positive pressure increases the minute volume of respiration and prevents or corrects the respiratory depression responsible for the respiratory acidosis

Smoking Smoke, regardless of its source, is irritating to the mucosa of the entire respiratory passageway. The sensitivity varies among individuals, but in the presence of bronchial disease, the irritation from the smoke is greater than in the normal, and it may be that normal mucosa does not exist in the habitual smoker. The elimination of tobacco smoking by the patient with bronchial disease is an important recommendation Many patients are seen with chronic bronchitis in whom smoking is the

with high velocity exsufflation is frequently a *valuable procedure for prevention of serious* retention of secretion and for active treatment.

If frequent aspiration is required, tracheotomy is indicated, and may be a life-saving procedure Prophylactic tracheotomy is justified in the poor-risk elderly patient following extensive thoracic surgery.

Bronchiolitis

Acute Bronchiolitis

Acute bronchiolitis is an inflammatory disease of the respiratory tract predominately involving the smallest bronchi and bronchioles, and characterized clinically by dyspnea, tachycardia and emphysema. There is confusion concerning the nature of this disease as to whether it is a true bronchiolitis or whether or not it is even a clinical entity. Terms applied to this disease include capillary bronchitis, pneumonitis, bronchopneumonia, obstructive emphysema and interstitial bronchopneumonia This physiologic and pathologic entity is sometimes confused with croup, acute laryngotracheobronchitis, bronchitis, asthmatic bronchitis, bronchial asthma and pneumonia

Etiology Although acute bronchiolitis may occur at any age, it is extremely rare except in infants and younger children, generally, under one year of age. It is most common in winter, fall and spring, and parallels the incidence of upper respiratory infections The most common organism cultured from the sputum is *Hemophilus influenzae*. Some workers have postulated that this is predominately a virus infection, and that the organisms represent secondary invaders Most of the common, pathogenic respiratory organisms have been cultured from the sputum

Symptoms and findings Bronchiolitis is generally preceded by symptoms of an upper respiratory infection characterized by rhinorrhea and hyperemia of the pharynx These symptoms may precede bronchiolitis from one to several days The onset of bronchiolitis is characterized by an increase in cough and an increase in respiratory rate, the temperature may be normal or slightly elevated. As the disease progresses, dyspnea and restlessness appear, the heart rate is increased, cyanosis occurs, and the patient becomes septic and may become comatose. Fever generally occurs on the second or third day and is usually in the neighborhood of 101F, although temperatures as high as 104F. may be observed. *Physical examination* reveals rhinorrhea and hyperemia of the pharynx. The respiratory rate is usually rapid, and may be as high as 100 per minute. The heart rate is generally very rapid and, in the infant, may exceed 200 The patient is dyspneic and may be restless or comatose. The chest is generally hyperresonant, although areas of decreased resonance may be found. The breath sounds are generally distant Expiratory wheezes are usually present and not particularly loud, although occasionally they are heard at the open mouth Rather fine expiratory rales are usually present, and, occasionally, coarse rales are heard over the tracheal and bronchial areas

The hemoglobin and red blood counts are normal The white count may or may not be elevated early, but is generally elevated during the later stages of the disease, and particularly if secondary infection occurs Bacteremia is an uncommon complication.

Roentgenologic examination is characterized by the appearance of a generalized emphysema throughout both lungs. Transient areas of patchy atelectasis and occasionally a lobar atelectasis are observed, but generally disappear during the course of the disease. The diaphragms are depressed and flattened, and their excursions are reduced, as is seen in patients with emphysema regardless of etiology An increase of bronchovascular markings is frequently observed.

Pathologic physiology. The gross findings at autopsy consist of emphysema and patchy areas of atelectasis Microscopic examination reveals the bronchioles to be most affected The findings consist of infiltration with lymphocytes, plasma cells and occasional polymorphonuclear leukocytes The infiltration may extend into the interstitial tissues, and sloughing of the mucosa is also observed. The condition is characterized by marked variation in the degree of changes throughout the bronchioles; some bronchioles show very minimal changes; others, quite

smoking is stopped. Some of these patients may complain of a severe cough on arising in the morning, and that the first cigarette assists the elimination of the accumulated secretions.

This type of patient is frequently made worse temporarily, if the smoking is stopped suddenly, but often is benefited eventually by elimination of the smoke. The smoke serves as a stimulant to the bronchial glands, and the secretions are thinned by the activity of the glands. (Gradual elimination of smoking is advantageous, but the psychologic problems of breaking the habit may be intensified.)

The response to the cessation of smoking is dependent on the sensitivity to the smoke, the type, extent and duration of the bronchitis, and perhaps to other factors which are not recognized. Many patients mention that they have stopped smoking for a week or a month and have noted no improvement. The response to the cessation of smoking may require prolonged time before the beneficial effects are noted. (The patients' symptoms may not be produced by bronchitis as much as by other physiologic abnormalities). The indication still exists for the elimination of the smoke, and if it does no more than slow the progress of the pathologic state, it is well worth the effort. The psychologic effect on the patient, in itself, may be valuable because it forces him to recognize and control a habit which he has probably known for sometime as harmful, but refused to recognize it as such, and take the appropriate measures required for its elimination.

Postoperative Bronchitis

Postoperative bronchitis is usually of the suppurative type and is usually an exacerbation of a preceding bronchitis. This complication is unusual in the absence of cough and increased sputum. The history of coughing in the morning on arising is significant. The incidence is much higher in patients who aspirate secretions during surgery because the secretions irritate the bronchi and produce inflammation. During the immediate postoperative period, suppression of the cough reflex occurs as a result of the slow recovery from the anesthesia plus sedation and narcotics and shock which have a depressant effect on the respiration. In addition to this, the pain of coughing forces the patient to suppress the cough. The administration of atropine and atropine-like drugs, which have a suppressing effect on the bronchial secretion, contributes to the condition. Atropine reduces the amount of the normal secretion, but in the presence of an exudate the secretions are thickened by the reduction in the diluent action of the bronchial secretions. These factors all contribute to the retention of bronchial secretions and to bronchial obstruction.

The prevention of this condition involves, during the preoperative period, the recognition and definitive treatment of bronchitis. During the operative period, the toilet of the tracheobronchial tree is extremely important. During the postoperative period, the avoidance of atropine and the use of minimal doses, if any, of sedative and narcotic drugs are important. The encouragement of voluntary coughing is started during the preoperative period, and its importance is impressed on the patient. During the postoperative period, humidity therapy, binders to the chest or abdomen and manual support for the chest may be extremely helpful in encouraging and supporting the cough. Frequent changes of position and voluntary deep breathing are important. The frequent turning of the patient and the stimulation of respiration by the inhalation of carbon dioxide, which also stimulates the flow of bronchial secretion, are effective. The administration of oxygen in the prevention of hypoxemia is important, but humidification of the oxygen is essential.

Stimulation of respiration by inhalation of carbon dioxide also promotes flow of bronchial secretions, but in the presence of respiratory depression it is contraindicated because of the already high blood carbon dioxide tension. Intermittent positive pressure breathing on inspiration causes hyperventilation and blow-off of carbon dioxide and is one of the most effective measures in the prevention and treatment of bronchopulmonary complications.

Bronchial obstruction and atelectasis—either patchy, lobar or massive—are the result of retention of bronchial secretions. Immediate aspiration of secretion by catheter or bronchoscope is indicated. Inspiratory positive pressure

second, following the inhalation of irritant substances; and third, unknown. Bronchiolitis obliterans has been reported as a complication of influenza, pertussis, bronchitis, acute bronchiolitis, pneumonitis and the pneumonias. Although many of the irritating gases and fumes are etiologic factors, the fumes of the oxides of nitrogen are the most common.

Pathologic physiology. Bronchiolitis obliterans may be divided into three fairly distinct stages. The first stage of the disease is that of the etiologic condition In cases due to the inhalation of irritant fumes, there is destruction of the epithelial surface of the bronchioles with involvement of the bronchiolar wall of varying degrees, depending on the severity of the process Fatalities in this stage generally reveal pulmonary edema, necrotizing lesions of the tracheobronchial mucosa, and involvement of the alveoli Cough and chest pain vary in this stage The obstruction is more marked on expiration because of the expiratory narrowing. Expiratory wheezes and rales may be present. Localized areas of emphysema and atelectasis are more common than involvement of entire lobes Chest x-rays display a patchy mottling along the course of the bronchi with prominence of the bronchovascular markings and congestion

The second stage is that of resolution of the disturbances of the first stage Improvement in the symptoms and findings is noted This stage lasts for a few days to a month or more The roentgenograms may disclose the degree and progress of the improvement

The third stage is characterized by the formation of granulation tissue, connective tissue and fibrosis, involving the bronchioles These changes produce progressive narrowing of the lumen and, finally, obliteration. It is characterized by progressive intractable dyspnea, tachycardia, cyanosis and death. Cough may be severe, with the production of blood-tinged sputum. It is during this stage that the diagnosis is usually made in the cases following bronchopulmonary disease. In this type, the disease may be localized to one part of the lung. The obliteration of the lumen may predispose to lung abscess or bronchiectasis, proximal to the occlusion. Infection and retention of secretion may predominate in the involved area and, finally, require resective surgery.

Treatment. Supportative therapy, humidity, oxygen and positive pressure for the pulmonary edema are useful in the first stage. Antibiotic therapy to control and prevent secondary infection is valuable. In the third stage, treatment is ineffectual.

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marked changes; and areas of bronchopneumonia may be observed

The physiologic disturbances which occur in this disease are primarily related to the expiratory bronchial obstruction which produces the characteristic picture of emphysema or hyperdistention of the lung Due to the inflammatory process, transient areas of complete obstruction occur and produce atelectasis The interference with the air movement produces the predominant picture of hypoxemia, with tachycardia and cyanosis in the more severe cases Death is hypoxic in nature, and the toxemia may be contributory.

The cardiac load is increased by the hypoxemia and toxemia, and perhaps by resistance to pulmonary blood flow Henderson[5] has reported abnormalities observed in the electrocardiograms of infants with bronchiolitis These consisted of abnormalities in T1, T2, displacement of the S-T segment, with rare abnormalities in rhythm. He found these abnormalities to disappear as the infants recovered

Treatment Bronchiolitis generally is a self-limited disease, and the therapeutic problem consists in maintaining the patient in the best possible condition. Although antibiotic therapy has not altered the course of this disease, it is still a valuable adjunct to the treatment It undoubtedly prevents secondary infection and reduces the incidence of complications resulting from this phase of the involvement

The relief of the hypoxemia is extremely important, and consists of the administration of high oxygen concentrations. High humidity and water aerosol therapy are combined with oxygen therapy. Depending on the severity of the hypoxemia, oxygen concentrations of 40 or 50 per cent to 80 or 90 per cent are used Because of the toxemia, the heat regulatory mechanism may be inadequate, and this in combination with the fever makes the use of high temperatures definitely contraindicated

The intramuscular administration of epinephrine may produce transient improvement in the respiratory obstruction This is a valuable threapeutic test, and if improvement results, ephedrine and bronchodilator aerosols are used.

Sedation, if used at all, is employed with extreme caution. In some cases there are rapidly changing clinical conditions. At one time the patient may be extremely restless, and a few minutes later show definite signs of depression. The administration of a sedative drug to control the restlessness may have a deleterious effect, if the condition changes to one of depression or coma.

If fever occurs, every reasonable effort should be made to reduce it. The use of a cold water blanket is probably the most efficient means. This reduction in fever reduces the metabolic rate, reduces the minute volume of respiration, and, thereby, benefits the patient.

An adequate water balance is *important*. Intravenous fluids should be administered with extreme caution because the stress placed on the cardiovascular system predisposes to pulmonary edema especially in the presence of hypoxemia and respiratory obstruction

Expiratory positive pressure in a sense may be self administered, as shown in certain patients by the occurrence of a grunting type of expiration. This suggests the therapeutic use of intermittent positive pressure breathing, but I have not had the opportunity to use it

Bronchoscopy is usually of little value because the disturbance in physiology is beyond the reach of the bronchoscope and the aspirators Bronchoscopy is difficult for these extremely sick patients, and is therefore thought to be contraindicated. Bronchoscopy in the presence of a lobar atelectasis in acute bronchiolitis has been disappointing, and in some instances patients have become worse Tracheotomy for the aspiration of secretion or for the relief of the bronchiolar obstruction is similarly ineffectual, and emphasizes the value of self-administered expiratory positive pressure

Bronchiolitis Obliterans[7]

Bronchiolitis obliterans is an inflammatory disease of the bronchioles characterized by bronchiolar obstruction and dyspnea. The term chronic bronchiolitis generally refers to the chronic stage of bronchiolitis obliterans, either generalized or localized, and usually is of the milder type.

Etiology. The etiology is classified: first, a complication of bronchopulmonary infection,

TABLE 1 —Methods of Study and Ventilatory Measurements in Pediatric Age Groups

	Infants	Toddlers (1 to 6 yr)	School Children (7-12 yr)	Adolescents (13 yr plus)
Tidal Volume (ml)	20	150-250	250-600	450-650
Functional Residual Capacity (ml)	100*	400-1000	700-2000	1500-2400
Pulmonary Function Tests	Pressure-Flow Studies	Spirometric Studies Mixing and Distribution Studies		
	Pneumotachograph			

* From Berglund and Karlberg, ref. 7, Chapter 32

using a small 9 L. capacity Collins spirometer (FIG 2B) Maximum breathing capacity is of little value in children under the age of 8 years; but in children more than 10 years of age the capacity can be measured using a 100 L. Douglas bag with a low-resistance, high-velocity valve, during a 15 second interval

Studies of intrapulmonary mixing and distribution are undertaken at the time of measuring the functional residual capacity. The ratio of the volume of ventilation required to clear the lungs of nitrogen to the volume being ventilated (the FRC) is an indication of the efficiency of ventilation, or clearance equivalent.[11] In many instances the test may be more important than the volumetric determinations (FIG. 2C). In children, the test allows comparisons between those with different lung volumes, or in the same child whose lungs have changed as a result of growth Normal values for the clearance equivalent in adults have shown a minimum relationship to age, therefore, the average values of 15 L of total ventilation per liter of lung volume, or 8 L of alveolar ventilation per liter of lung have been used in appraising efficiency of ventilation in children The standards for evaluating the lung volumes and the maximum breathing capacity are taken from the tables given by Ferris and co-workers[2, 3] Estimated residual volume is considered as no higher than 25 per cent of vital capacity.

Ventilation has been simplified somewhat to represent the type of impairment (FIG. 3). Three main factors are involved: (1) flow resistance in the airways, (2) elastic forces of the lungs themselves and (3) nonpulmonary forces, producing movement of the lungs and thorax.

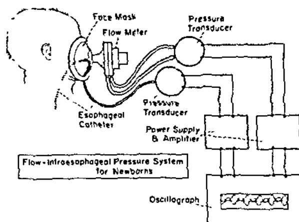


FIG 1 —*Diagram of flow-intraesophageal pressure system in newborn infant*

The types of ventilatory impairment are classified on a causal factor basis The respiratory conditions most frequently encountered in infants and children vary considerably from those in adults, as noted in TABLE 2

ABNORMAL PULMONARY VENTILATION IN INFANTS

"Abnormal pulmonary ventilation" as a term encompasses the unexpanded lung of the newborn, whether it be completely unexpanded or partially expanded, i e , atelectasis, the hyaline membrane syndrome and aspiration with associated collapse. In the normal full-term infant, the bronchioles are patent as are the alveolar ducts and alveoli, and the capillaries are well filled The physiologic tracing of such an infant (FIG. 4) at the age of 18 hours, reveals

Bronchopulmonary Diseases in Infants and Children

The Physiologic, Pathologic and Clinical Relationships

By ROY F. GODDARD, M.D

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THE physiologic aspects in bronchopulmonary diseases in infants and children have not received sufficient emphasis in the past, since accurate pulmonary studies in children are technically difficult to perform, and their interpretation must be limited to the meager comparative data now available in the pediatric age groups. Physiologic testing has been limited to air flow, lung volumes, general respiratory competence and distribution Fortunately, in the evaluation of data, clinical findings have often suggested a parallel with the physiologic findings, and the pathology in similar cases has offered important confirmatory evidence of the basic disturbance An interesting feature has been the response of certain cases to physiologic treatment, further amplifying the cause or causes of the underlying disturbance

Special technics are frequently required to carry out physiologic studies in infants and children; examples of the methods used in infants and children are outlined in TABLE 1 The pneumotachogram for recording the velocity of air flowing through the airways in infants is made with a miniature flow meter attached to a plastic mask which covers the patient's mouth and nose with a pneumatic seal. The flow velocity is converted to electrical impulses by a pressure transducer, amplified and visualized on an oscillograph (FIG. 1). Intraesophageal pressure changes are transmitted by a water-filled, open-end esophageal catheter to a pressure transducer, amplified and recorded simultaneously with the flow pattern on an oscillograph.

The procedures used for studying children are identical with those for adults, except for a few modifications necessitated by the small tidal volumes and fast respiratory rates The mouth piece and valve assembly should have minimal dead space, or the child will rebreathe a volume approaching his tidal volume, and as a result the CO_2 would build up to an uncomfortable level. In addition, the alveolar ventilation is a much smaller proportion of the total ventilation, thus, the clearance equivalent is no longer valid as an index of true mixing and distribution in the lungs

Pneumotachograms have served as a rapid screening evaluation of obstructive impairment, with determinations from the peak of inspiratory and expiratory flow, the length of exhalation and the time interval from the peak inspiratory to the peak expiratory flow [8] Forced vital capacities can usually be obtained in toddlers by making a game out of "blowing it up" as fast as possible, thus creating interest and obtaining a more effective test, especially when accomplished by several siblings in the same family (FIG. 2A). The first-second forced expiratory capacity ($FEC_{1.0}$) is the most important, since many times a 3 second value cannot be obtained The timed forced expiratory capacities are probably the most accurate determination of obstruction in children, as many children with severe pulmonary disease are unable to perform a maximum breathing capacity test. In the past year, development of a special nonrebreathing valve, with an approximate dead space of 25 ml, has allowed further studies of volumetric and diffusion measurements in the toddler or preschool child (ages 2 to 6 years), when sufficient co-operation has been obtained

Conventional studies of lung volumes are carried out in children past the age of 6 years,

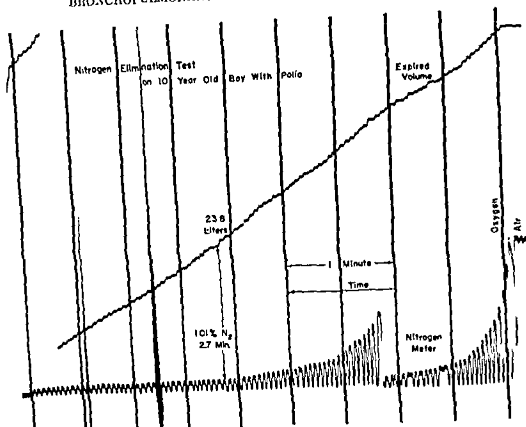


Fig 2—(C) Nitrogen elimination test in a boy, 10 years of age, with poliomyelitis

exhibit a prominent lobular pattern. (Fig 5B). In the present case, the lungs were not expanded at post-mortem examination, and the bronchiolar epithelium was thrown into numerous folds. Clinically, in such infants, the breathing is usually rapid and shallow. There may be minimal sinking of the upper chest as the abdomen rises; expiratory grunting is rare.

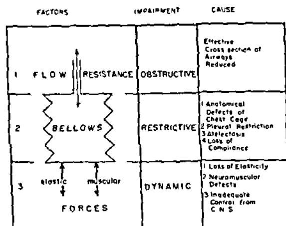


Fig 3—Ventilation chart (Dis. Chest, 1956[8])

Hyaline Membrane Syndrome

The condition known as "resorption atelectasis" is usually seen in the hyaline membrane syndrome (discussed in Chapter 32), and may result in a low tidal volume with low compliance This, combined with high flow resistance, greatly increases the work of breathing. Fatigue with inadequate central nervous system control may cause dynamic impairment, represented by the see-saw movement depicted in the flow tracing (Fig. 6). In this syndrome, a prominent acidophilic hyaline membrane is present in the lumen of the bronchiole, in the lining of the terminal alveolar duct and many of the collapsed alveoli (see Fig. 7, Chapter 32) Respiratory distress in this case became increasingly evident two to eight hours following birth. Symptoms included restlessness, cyanosis, rapid respiratory rate, audible expiratory grunting, marked intercostal and xyphoid retraction and the so-called see-saw sinking of the upper chest as the abdomen rises. Chest x-rays of such infants reveal a reticulogranular or miliary-like appearance (see Fig 6, Chapter 32).

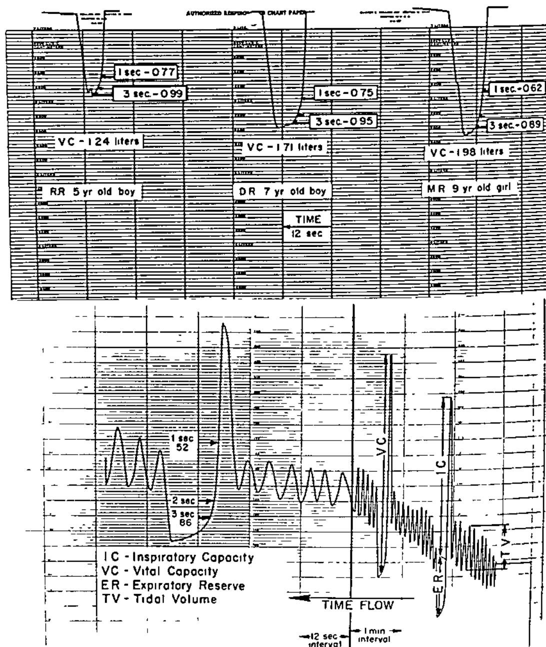


Fig 2—(A) *Above.* Illustration of forced vital capacity of three asthmatic siblings (B) *Below.* Spirogram of boy, 12 years of age, with manifestations of asthma

a tidal volume of 20 3 ml., respiratory rate of 47.1 per minute, a respiratory minute volume of 956 ml. and a compliance of 4.1 ml /cm H_2O. The work of breathing is 7,280 Gm. cm / L , of which 3,300 Gm. cm /L. (or 45 per cent) is expended for overcoming the elastic resistance of the lungs themselves (Elastic work usually averages about 55 per cent of the total work.) Clinically, there is synchronous expansion of the chest and abdomen without signs of retraction or expiratory grunting

In premature infants, although there is no definite obstruction, greater pressures are required to expand the doughy, soggy, unexpanded lungs. The flow-pressure tracing (Fig 5A) shows a shorter and more abrupt pattern; compliance values are low. Fatigue, caused by the increased work of breathing, coupled with immature central nervous system mechanisms, may produce dynamic impairment. The lungs of premature infants often show small unexpanded alveoli, lined with cuboidal cells, and

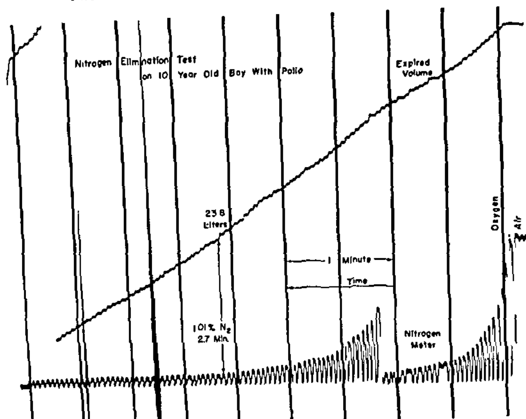


FIG 2—(C) Nitrogen elimination test in a boy, 10 years of age, with poliomyelitis.

FACTORS		IMPAIRMENT	CAUSE
1	FLOW RESISTANCE	OBSTRUCTIVE	Effective Cross section of Airways Reduced
2	BELLOWS	RESTRICTIVE	1 Anatomical Defects of Chest Cage 2 Pleural Restriction 3 Atelectasis 4 Loss of Compliance
3	elastic / muscular FORCES	DYNAMIC	1 Loss of Elasticity 2 Neuromuscular Defects 5 Inadequate Control from C N S

FIG 3—Ventilation chart (Dis Chest, 1956[8])

exhibit a prominent lobular pattern. (FIG 5B). In the present case, the lungs were not expanded at post-mortem examination, and the bronchiolar epithelium was thrown into numerous folds Clinically, in such infants, the breathing is usually rapid and shallow. There may be minimal sinking of the upper chest as the abdomen rises, expiratory grunting is rare.

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School child and Adolescent	Asthma and Chronic cough, bronchitis, bronchiectasis, poliomyelitis

* Table is not all inclusive; anoxia and congenital anomalies are not listed Frequently, conditions listed for infants occur in toddlers, those listed for toddlers may occur at later ages.

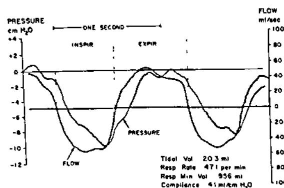


FIG 4—Flow-pressure tracing of a normal full-term infant, age, 18 hours, weight, 7 pounds, 13½ ounces

Pulmonary Hemorrhage

Another condition which offers considerable obstructive and restrictive impairment in infants is pulmonary hemorrhage In this condition, there is extremely poor tidal volume exchange, high inspiratory and expiratory resistance, low compliance, and increased work of breathing (FIG. 7A). If the infant does not succumb to anoxia, cardiac failure may ensue The photomicrograph in FIGURE 7B reveals massive fresh hemorrhage, filling and distending the alveoli and the presence of blood cast in the bronchioles, with thick alveolar septa and focal areas of atelectasis Distress in thi 7 month old, premature infant first becam evident at 24 hours with rapid, shallow respira tions, moderate intercostal and xyphoid retrac tions, and audible grunting. At 60 to 72 hour the child developed sudden episodes of irregula respiration, with apneic periods, became dusk and deteriorated rapidly, with death ensuin at 90 hours Death probably resulted from com bined cardiopulmonary failure

CROUP, BRONCHIOLITIS AND PNEUMONIA

Croup

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In croup, the mucosa extending from th larynx to the bronchi is covered by patchy area

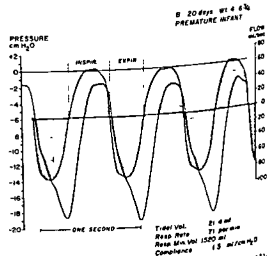


FIG 5—(A) Flow-pressure tracing of prematur infant, age, 20 days, weight, 4 pounds, 6¾ ounce



Fig 5 —(B) Photomicrograph of lungs of a premature infant, illustrating limited expansion of the pulmonary tissue

of exudate, composed of fibrin, some mucous, round cells, and polymorphonuclear leucocytes There is a variable degree of mucous-gland degeneration. Fibrinous exudate may be present with small submucosal abscesses, particularly in H-influenza croup. Accompanying the hoarse voice and brassy cough are the signs of upper respiratory obstruction mentioned above When the trachea is involved, there may be loud, moist rales or rhonchi, if the bronchi are involved, patchy areas of fine, moist or sibilant rales may be present. The respiratory rate is usually elevated; the diaphragms are high and show maximal excursion.[12]

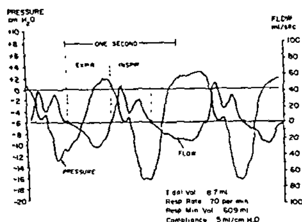


Fig 6 —Flow-pressure tracing of infant with hyaline membrane syndrome, age, 36 hours; weight, 3 pounds, 14 ounces

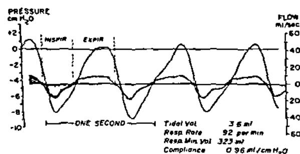


Fig 7.—(A) Flow-pressure tracing of infant with pulmonary hemorrhage; age, 47 hours; weight, 2 pounds

Bronchiolitis

While croup or laryngotracheobronchitis is primarily an inspiratory difficulty, bronchiolitis in the infant is more of an expiratory problem. Figure 8A demonstrates this in a two month old infant with considerable obstructive impairment, and trapping of air, leading progressively to hyperaeration. Expiration was almost twice as long as the period of inspiration (inspiration 0 7 second, expiration 1.3 seconds). During each inspiratory phase, 66 ml. of air entered the lungs while only 63 5 ml. left during

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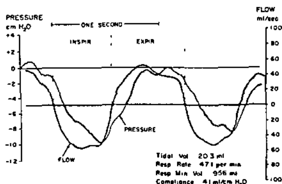


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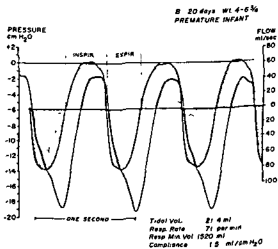


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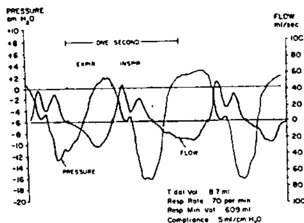


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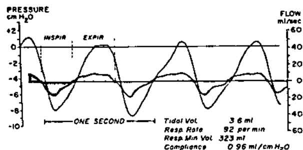


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FIG. 5.—(A) Flow-pressure tracing of premature infant, age, 20 days; weight, 4 pounds, 6¾ ounces



FIG 8 —(B) Photomicrograph of bronchiolitis, showing occlusion of bronchiole by inflammatory cells and exudate

cent of neonatal deaths Clinically, the infant may be listless and refuse to nurse Breath sounds may be normal, but the roentgenograms usually show a diffuse pneumonic involvement.

Bronchopulmonary Diseases in Children

Asthma

Asthma occurs at any age in infants and children The condition in older children is similar to the syndrome in adults, with an acute, recurrent bronchial inflammation, obstruction and hyperaeration The severity of the symptoms and the physiologic manifestations are greatly influenced by the duration of the condition Considerable obstructive impairment is usually present as noted in a 9 year old girl with a reduced 1 second expiratory capacity of 66 per cent of total vital capacity and a maximal breathing capacity of 13 L. per minute (FIG 9A). In this child, obstructive and restrictive impairment have resulted in a decrease of the vital capacity to 33 per cent, with a corresponding increase in the residual volume [illegible] than 18 In effect, these

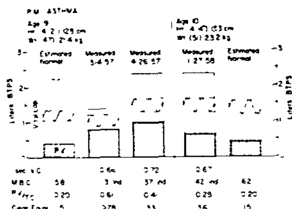


FIG 9 —(A) Pulmonary function studies in asthmatic girl, 9 years of age, before and after IPPB therapy.

measurements signify a pulmonary cripple at the time of the first test.

Clinically, the 9 year old child described above was asthenic and apprehensive with mild cyanosis of the lips and nail beds. Her thorax was emphysematous in type, with an increased anteroposterior diameter, and hyperaeration of the bases of the lungs. Respirations were rapid and shallow, with audible expiratory wheezing. Frequently, prodromal symptoms in such cases include sneezing, nasal discharge, tearing and cough.[5]



FIG 7 —(B) Photomicrograph of pulmonary hemorrhage, showing massive fresh hemorrhage in alveoli and bronchioles

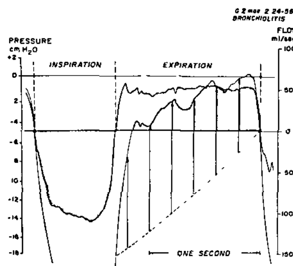


FIG 8 —(A) Flow-pressure tracing of two month old infant with bronchiolitis

expiration. The peak flow during inspiration was 110 ml. per second, 50 ml. per second on expiration. Compliance in this two months old infant was 4.8 ml./cm. H_2O. The pressure required to overcome the expiratory resistance was increased fivefold

The pathology of bronchiolitis shows almost complete occlusion of the bronchioles by acute inflammatory cells. The alveolar ducts and the alveoli remain clear. (FIG. 8B). There is usually rapid onset of respiratory distress with low-grade fever, pallor and increased respiratory rate, breathing is shallow, with intercostal and subcostal retraction Breath sounds are usually inaudible Following inhalational therapy, rhonchi are usually heard, together with sibilant rales throughout the lungs. Upper respiratory obstruction is not often present. Some degree of hyperaeration may be present as suggested by roentgenograms of the chest.

Pneumonia

Pneumonia in infants may be due to several causes such as aspiration of infectious amniotic fluid, irritative pneumonia due to aspiration of sterile amniotic fluid, premature rupture of the fetal membranes, long labors, complicated deliveries and cesarean sections [9] Atelectatic, congested and edematous lungs of asphyxiated infants coupled with fetal anoxia contribute to lowered resistance to infection. The invading organisms are usually staphylococcus, streptococcus or colon bacilli in infants, and the pneumococcus in the older age group. Bronchopneumonia is not only a primary cause of death during the neonatal period, but in certain instances it is contributory in association with other conditions It is present in about 10 per

($1 FEC_{1.0}$) is low and delayed, and the maximum breathing capacity may be low. The pulmonary volumes may be normal, but sometimes with uneven pulmonary mixing. The pathologic picture is usually one of thickening of the bronchial mucosa with some obstruction, vasodilation, congestion, edema and limited activities of the ciliated cells.

Bronchiectasis

Several conditions may lead to bronchiectasis in children, as in the case of cough and bronchitis; predisposing conditions have been labeled as pneumonia, pertussis, pulmonary collapse and chronic bronchitis. Physiologic difficulties may be related to the severity of the disease process. The respiratory rate may be increased, early in the disease there is moderate obstructive impairment with decreased forced expiratory capacity, and decreased maximum breathing capacity, usually with very little disturbance in ventilatory efficiency (Fig 10A).

The pathology of bronchiectasis is more extensive than in bronchitis, with ulceration of the wall, affecting the elastic bronchial tissue and later the cartilage. Fibrosis may occur later in the disease process, along with permanent collapse of alveoli in some areas, and emphysematous changes in others Tubular dilatation is the most common type of bronchiectasis in children[4]

The clinical features of bronchiectasis are usually bouts of coughing, with or without sputum (sputum often may be swallowed) Hemoptysis is rare, there may be associated asthmatic symptoms Most children are underweight, and many have abnormal chest deformities There is clubbing of the fingers in a significant number of the patients Physical signs in the chest vary; the most useful diagnostic finding is the presence of localized rales on deep inspiration over the affected areas of lungs Sinusitis is frequently associated with bronchiectasis The chest x-rays of a 9 year old girl showed fusiform dilatation (Fig 10B) of a moderate degree, involving the lower lobe bronchi, bilaterally There had been a chronic cough of two years' duration, following recuperation from pneumonia and pertussis

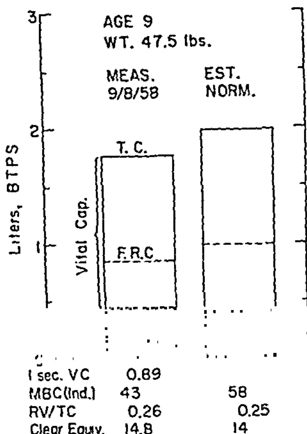


Fig. 10 — (A) Pulmonary function studies of early bronchiectasis in girl (M M), 9 years of age

Advanced bronchiectasis may occur in the second decade of life with considerable deterioration in pulmonary function This was evident in a 10 year old Indian boy (Fig 11A) suffering from repeated respiratory infections, bouts of chronic cough, and failure to gain weight He showed an increase in his residual volume to 41 per cent, reduction of the $FEC_{1.0}$ to 59 per cent of total, with a maximum breathing capacity of 49 There was considerable impairment in ventilatory efficiency, with a nitrogen clearance equivalent of 40 8 His bronchogram (Fig. 11B) revealed cylindrical and saccular bronchiectasis of the lower lobe basilar segmental bronchi. Such patients should be considered for pulmonary resection or lobectomy. However, a point of reversibility of the process has been argued,[4] but thorough medical-physiologic therapy should be given a trial.

Mucoviscoidosis

Mucoviscoidosis (mucoviscidosis), more commonly referred to as fibrocystic disease of the



FIG 9—(B) Photomicrograph showing obstruction, chronic inflammation and hyperaeration *in asthmatic boy, 3 years of age*

The pathologic picture of asthma in children is characteristic (FIG. 9B) The bronchioles are filled with tenacious mucus and chronic inflammatory cells; there is proliferation of the bronchiolar epithelium, peribronchiolar inflammation and hyperaeration are also present The x-rays and post-mortem examination may demonstrate gross hyperaeration and cor pulmonale.

Chronic Cough

Chronic cough in children is more of a symptom complex than a disease entity The clinical picture, usually, is that of a child who has developed a dry, nonproductive cough of several months' or years' duration, bronchiectasis may have been suspected. Physiologically, pneumotachographic tracings may show some minimal obstructive impairment with shallow inspiratory and expiratory exchange.[6] The forced expiratory capacities ($FEC_{1.0}$, $FEC_{3.0}$) may be slightly reduced, otherwise pulmonary function tests rarely show restrictive or ventilatory impairment The x-rays reveal increased bronchovascular markings, otherwise the findings are entirely negative, including bronchograms. The pathologic feature of chronic cough is bronchial irritation, with edema.

Bronchitis

Bronchitis of long duration may become one of the most serious problems in childhood Usually the cough is accompanied by production of sputum, depending on the type and severity of the inflammation It is possible that "chronic cough," bronchitis and bronchiectasis are progressive stages of the same "end-respiratory process." The clinical picture of bronchitis usually is one of progressively severe attacks of bronchial coughing with increasing production of bronchial secretions Associated symptoms are fever, coryza and lack of weight gain, causing frequent absence from school Chest x-rays usually show some increase in bronchovascular markings, and frequently sinusitis may be present.

Physiologically, moderate obstructive impairment is present, with a slowing of the maximum speed of inspiration and expiration, particularly during the expiratory phase An evaluation of the air flow rates permits an approach to the problem of determining the significance of bronchitis. Frequently a simple pneumotachogram may be of considerable value in such an air flow evaluation. In many instances, the forced expiratory capacity

the nonpulmonary forces concerned in ventilation—the chest wall and CNS control), except during the acute phases when obstructive impairment is present, due to inability to expectorate secretions from the bronchi. The physiologic findings in a 10 year old boy, one year after an acute attack, showed a reduction in the total and vital capacities, an increase in the residual volume and slight impairment of the ventilatory efficiency (FIG. 13). Dyspnea and obstructive phenomena, suggesting emphysema, had been present during the acute phase, together with paralysis of the muscles of the thorax and extremities. Physiotherapy was remarkably satisfactory, showing improvement of pulmonary function both on a volumetric and functional basis.



FIG 11 —(B) Bronchogram, showing cylindrical and saccular bronchiectasis of lower basilar segments (case, IIa)

Emphysema

Emphysema in children is best divided into pre-emphysema, true secondary emphysema and congenital lobar obstructive emphysema.[9] Many etiologic factors have been postulated for congenital lobar emphysema: regional obstructive emphysema and pulmonary air cysts; congenital anomalies, including chondromalacia of the air passage structures, check valvular bronchial obstruction, pulmonary necrosis and trauma of birth; and vigorous attempts at resuscitation. In congenital emphysema, pulmonary function is altered, particularly in the area in which the main obstruction occurs. Symptoms

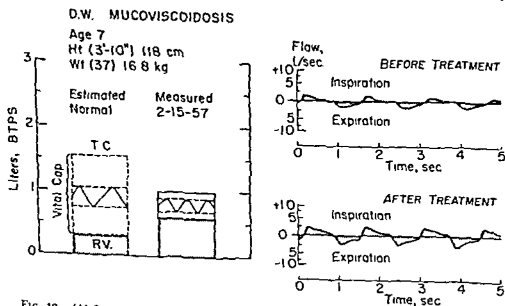


FIG. 12 —(A) *Left* Pulmonary function studies in 7 year old girl with mucoviscoidosis (B) *Right* Pneumotachograms in the same patient.

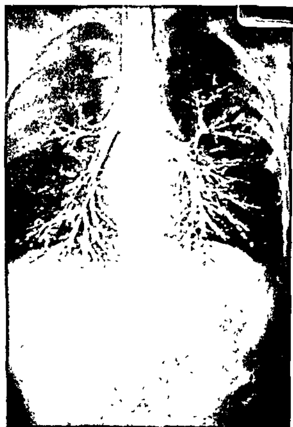


FIG 10 —(B) Bronchogram of fusiform bronchiectasis, lower lobe, (case 10a)

pancreas, involves the exocrine glands throughout the body, including the sweat glands, tear glands, digestive glands, and the mucous-secreting glands in the lungs It can also produce any type of lung disease—abscess, atelectasis, bronchiectasis, emphysema and associated cor pulmonale, and therefore results in the most serious respiratory problem in pediatrics

The physiologic impairment of fibrocystic disease is usually one of considerable obstructive distress with shallow inspiration, prolonged expiration and prolonged time intervals from the peak inspiratory flow to peak expiratory flow (FIG. 12B). Pulmonary function tests in this 7 year old girl showed marked reduction in the total capacity, the tidal volume and the vital capacity, with an increase in residual volume to 67 per cent of the total capacity. Nitrogen clearance showed extremely poor ventilatory efficiency. Oxygen saturation was extremely poor.

Gross examination of the lungs exhibits a tenacious, purulent exudate (in this case, *pseudomonas aeruginosa* and *staphylococcus*), filling the bronchi and bronchioles Atelectatic and emphysematous areas are present with some peripheral consolidation (FIG. 12C). Microscopically, occlusion of the bronchioles with cellular exudate is present along with peribronchiolar inflammation and emphysema (FIG. 12D)

The signs and symptoms of mucoviscoidosis are usually as follows. poor physical development, meager subcutaneous tissue, clubbing of the fingernails, mild cyanosis, dyspnea, frequent cough and fine to coarse rales heard throughout both lungs X-rays of the chest reveal "cotton fluff" stippling of the lungs, with the features of emphysema and in advanced cases, cor pulmonale. (FIG 12E).

Poliomyelitis

The ventilatory impairment in poliomyelitis is primarily dynamic in type (i e., involving

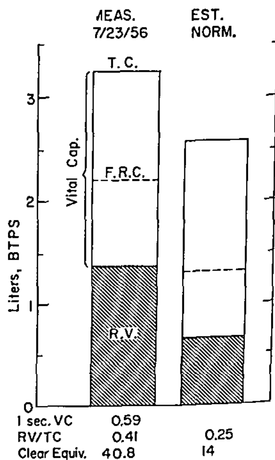


FIG 11.—(A) Pulmonary function studies in advanced bronchiectasis in boy (S G), 10 years of age, weight 63 pounds.

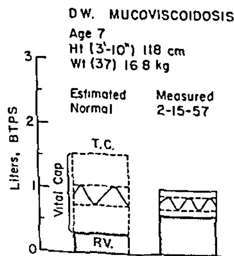
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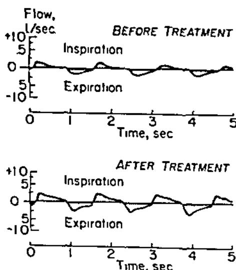


Fig 12—(A) *Left* Pulmonary function studies in 7 year old girl with mucoviscoidosis (B) *Right* Pneumotachograms in the same patient

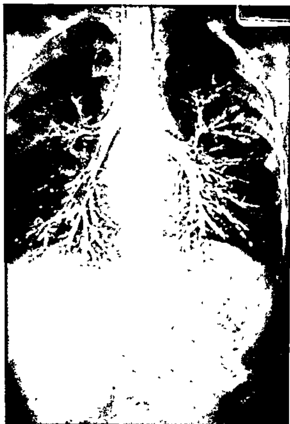


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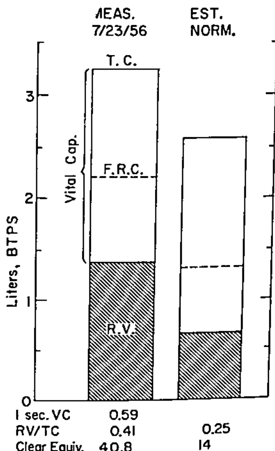


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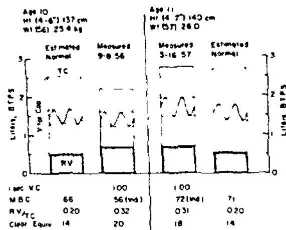
FIG. 12.—(E) Roentgenogram, showing "cotton fluff" appearance of pulmonary mucoviscoidosis, together with emphysema and cor pulmonale (case 12E)

structive emphysema. Pulmonary cysts are (usually) readily visualized by x-ray. Surgical intervention may become necessary in any of these three conditions.

True primary emphysema (obstruction, hyperaeration and destruction) does not exist in childhood. Pre-emphysema comprising obstruction and hyperaeration is seen in bronchiolitis and similar obstructive processes, usually accompanying acute inflammatory conditions. Such pre-emphysema may be reversible. Secondary emphysema (destructive component added) may result from long-standing or recurrent bronchopulmonary diseases, such as asthma, bronchiectasis and mucoviscoidosis.

Rare Conditions

Other pulmonary conditions in childhood interfere with ventilation, as for example, amyotonia congenita. The pneumotachograph in this condition usually shows abdominal type of breathing with rapid, short, high-peaked type of respiratory patterns.[6] Intercostal and subcostal retractions are usually evidenced clinically, suggesting poor muscle tone. In scleroderma, the total lung capacity and vital capacity may be within normal limits, however, the nitrogen clearance test may indicate reduced ventilatory efficiency.



	Estimated Normal	Measured 9-8-56	Measured 3-16-57	Estimated Normal
1 sec VC		100	100	
MBC	66	56 (wd)	72 (wd)	71
$RV/_{TC}$	0.20	0.32	0.31	0.20
Clear Equiv	14	20	18	14

FIG. 13.—Pulmonary function studies in a 10 year old boy (D.K.) with poliomyelitis, before and following physiotherapy.

Granulomatosis and giant cell pneumonia show obstructive and restrictive impairment, as well as poor ventilatory efficiency, and usually progress to a terminal state of bronchiectasis and emphysema, similar to children with mucoviscoidosis.

THE TREATMENT OF BRONCHOPULMONARY DISEASES IN INFANTS AND CHILDREN

Summary of Treatment

The representative cases of bronchopulmonary disease in infants and children, as de-

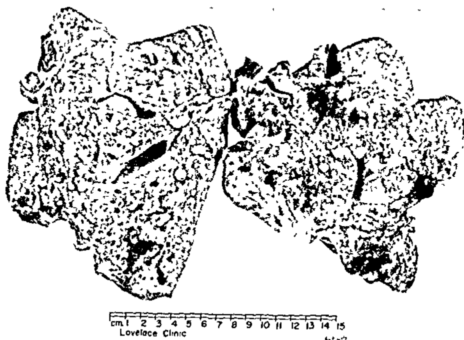


FIG 12—(C) Gross pathology of mucoviscoidosis, showing bronchi filled with tenacious, purulent exudate, with areas of atelectasis and emphysema (case 12a)



FIG 12—(D) Photomicrograph of pulmonary changes in mucoviscoidosis, showing occlusion of bronchioles, peribronchiolar inflammation and emphysema (case 12a)

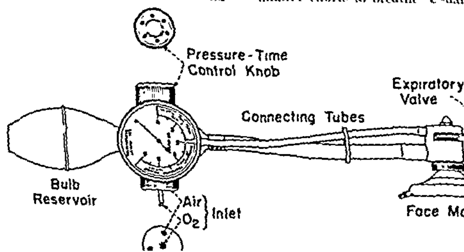
usually occur suddenly in the absence of infection and include dyspnea, cyanosis and wheezing. Lethargy, fever and asymmetry of the thoracic cage may be present, together with retractions, shift of the mediastinal contents, absent breath sounds or almost any pulmonary findings. When respiratory distress becomes progressively worse on conservative therapy, a presumptive diagnosis of obstructive emphysema should be considered Pneumomediastinum and pneumothorax, occurring independently or in combination, are well demonstrated by chest roentgenograms. Bronchoscopy may be helpful in ruling out regional or localized ob-

ventilation is required as the initial step. The general regimen includes augmented respiration, postural drainage, chemotherapy and bronchodilator drugs, detergents and enzymes administered by aerosol. Since this book is concerned primarily with the physiologic aspects, medical care per se is included only briefly in the summary of indicated therapy (TABLE 3).

Resuscitation and Augmented Respiration in Infants

Frequently in infants with abnormal pulmonary ventilation, requiring assistance in breathing and promotion of bronchial drainage, resuscitative measures may be called on as a means of augmenting respiration. Certain basic principles of resuscitation should be followed: (1) Establish a patent airway by gentle nasopharyngeal suction with the infant slanted downward (10 to 15 degrees) and the head hyperextended by use of a pad or diaper under the shoulders, (2) expand lungs by intermittent positive pressure, (3) promote adequate drainage by intermittent suction to keep airways clear of mucus and secretions, maintain postural drainage, (4) administer oxygen (up to 40 per cent) when indicated, (5) maintain temperature and humidity; (6) gastric lavage as required (premature infants, cesarean section cases, and for evidence of an excessive amount of amniotic fluid and debris), and (7) stimulants when indicated—chemical and

cutaneous or proprioceptive. Th should be accomplished immedi baby's condition does not improv minutes of birth, positive pressu applied. To achieve expansion ei itial resuscitation should start wi cation of a positive water pressur cm.[7] Such a pressure can be safely a 0.2 to 0.3 second interval when GBL (Goddard-Bennett-Lovelace resuscitator (FIG. 14A AND 14B 24 impulses are given in the fir resuscitation, allowing an expira of 0.4 to 0.8 second in order tha tion occurs and circulatory retu peded. Any mucus, meconium fluid, which may have been brou the lower respiratory tract with th velocity expiratory flow rates, moved by suction. Following init tion at these high pressures, the show some degree of expansion the infant takes a breath. (Frequ two impulses may be sufficient t piration.) Once satisfactory ex voluntary respiration have been pressure should then be reduced another 12 to 24 impulses, follow suction, finally, the pressure is 20 to 30 cm. of water. The ra pressure impulses is guided by who should synchronize the impu infant's efforts to breathe. Usual



scribed in this chapter, emphasize the relationship of physiologic disturbances to the pathologic process or condition. Because the interplay of mechanisms and infection frequently contributes to a poor prognosis, early evaluation and all-inclusive therapy is indicated

In the majority of instances, adequate drainage of bronchi and bronchioles with improved

TABLE 3.—*Summary of Indicated Therapy in Bronchopulmonary Diseases of Infants and Children*

Example	Type Impairment	Therapy Indicated
Premature infant	Restrictive ?Dynamic	Augmented Respiration*
Hyaline membrane syndrome	Obstructive Restrictive ?Dynamic	Maintain clear airways† Prevent resorption atelectasis Augmented respiration
Pulmonary hemorrhage	Obstructive Restrictive	Maintain clear airways Provide adequate oxygenation Prevent atelectasis and infection‡
Croup	Obstructive (upper)	Reduce laryngeal edema‡ Provide adequate oxygenation Prevent infection
Bronchiolitis	Obstructive (lower)	Clear airways (liquefy inflammatory exudate in bronchioles) Bronchiolar dilatation Combat infection§
Pneumonia	Obstructive? Restrictive	Provide adequate oxygenation Liquefy secretions Combat infection
Asthma	Obstructive Restrictive	Maintain clear airways Promote bronchial drainage Intermittent positive pressure breathing Prevent infection
Chronic cough Bronchitis	Obstructive	Bronchial dilatation and drainage Combat infection
Bronchiectasis	Obstructive Restrictive	Maintain clear airways Promote bronchial drainage Control infection Consider surgical excision
Mucoviscoidosis	Obstructive Restrictive	See asthma Combat atelectasis and bronchiectasis Control acute and chronic infections, prevent chronic anoxia Bronchoscopy as indicated
Poliomyelitis	Dynamic	Reconditioning of elastic and muscular forces Maintain clear airways Control infection

* Supplement infant's breathing with apparatus such as tank respirator in polio cases
[illegible] and frequent suctioning as needed
[illegible]ry agents.
[illegible]gents



FIG. 16 – Infant with bronchiolitis in croupette, receiving aerosol therapy

Inhalation Therapy

Croup, bronchiolitis and pneumonia in older infants are favorably treated by inhalation and aerosol therapy. This is usually provided in a mist atmosphere or environment which can be achieved in a croupette (FIG. 16). Fine droplet aerosols are also important in this age group and may require a special generator, such as the Mist-O_2 Gen apparatus, medicaments usually consist of a bronchodilator, detergent or anti-foam solution, and normal saline. Aerosol administration (particularly enzymes) may be combined with intermittent positive pressure breathing given via the GBL infant hand resuscitator or the Bennett IV-1 A infant respiration unit. Better hydration, which is important in treating these respiratory conditions in infants and children, can be achieved with inhalational therapy, oxygen can be added when indicated. Early diagnosis and initiation of this type of therapy has eliminated the need for tracheotomies and minimized morbidity and mortality in these once feared conditions. Croup today can be treated at home frequently by means of an air compressor, furnishing the force to run a nebulizer and produce the aerosol needed, and the combination of an antibiotic and steroid preparation (such as liquid Cortef) given orally.

Intermittent Positive Pressure Breathing in Children

In bronchopulmonary disease of older children with features of obstruction and restriction, it is necessary to maintain clear airways, promote drainage, control infection and prevent impending emphysema and cor pulmonale, as found in adults. Physiologic therapy includes respiratory exercises, if co-operation can be satisfactorily attained, and the use of intermittent positive pressure breathing treatments. Children from 1 to 5 years of age use the Bennett IV-4P or IV-3C pressure breathing units, modified from the TV-2P adult model.* These provide a greater flow sensitivity and less dead space in the connecting face piece attachment. Slow, deep breathing is desirable in order to avoid hyperventilation. As the child becomes adjusted to the positive pressure breathing technic, an aerosol mixture should be introduced through the nebulizer. Initial pressures of 8 to 10 cm. may be increased to 10 to 15 cm., depending on the age of the child and the response to treatment. Initial treatments range from 5 to 10 minutes; most routine treatments are of 10 minutes' duration; occasionally, some may be increased to 12

* Manufactured by Bennett Respiration Products, Inc., Los Angeles, California

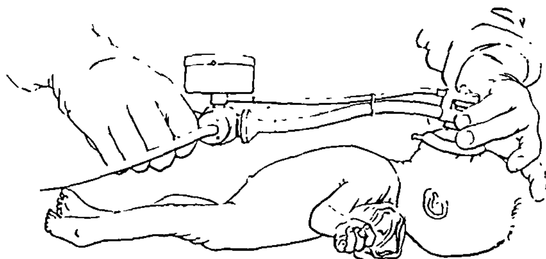


FIG 14 —(B) The application of GBL resuscitator to the newborn infant

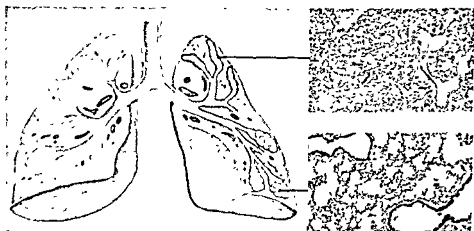


FIG 15 —The physiologic effects of intermittent positive pressure breathing in infants are suggested in the schematic drawing (1) Expansion of nonexpanded lungs of infants who do not breathe (2) Assistance in correction of partial atelectasis and anoxia (3) Promotion of bronchial drainage and prevention of resorption atelectasis.

responds to intermittent positive pressure resuscitation within the first 20 minutes, failure to do so frequently indicates intracranial hemorrhage or congenital heart disease. If a patent airway is initially achieved and maintained, expansion can be achieved via a face mask and thus the dangers associated with intratracheal suction and insufflation are minimized. When absolutely necessary, tracheal intubation should be performed initially and correctly without repeated manipulations. Subsequent periodic intermittent positive pressure resuscitation is based on the clinical course and improvement in physical and roentgenographic findings. There should be no hesitation to resuscitate (at these pressures) a baby who shows any degree of respiratory distress. (The physiologic basis for intermittent positive pressure breathing in infants is outlined schematically in FIG. 15) In addition to intrapulmonary positive pressure resuscitation, it is important to maintain ventilation in an incubator or respirator which will provide continuous augmented respiration, such as that reported by Donald and Lord.[1] A humidified atmosphere, produced by a nebulizer that will produce droplets fine enough (3 to 5 microns in diameter) to penetrate into the smallest bronchioles frequently will assist hydration and prevent secondary atelectasis due to the cohesive forces and surface tension factors present in the alveolar walls of the newborn.



FIG. 16.—Infant with bronchiolitis in croupette, receiving aerosol therapy

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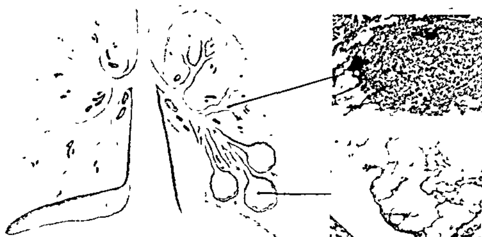


FIG 17 —The physiologic effects of intermittent positive pressure breathing in children are suggested in the schematic drawing *(1) Provide uniform alveolar aeration with improvement* in blood-gas exchange (2) Overcome spasm and promote bronchial drainage, decrease irritation and infection (3) Provide breathing exercise with improved muscle tone and compliance

minutes. The TV-2P Bennett therapy unit is used in children over the age of 6 years for giving inspiratory positive pressure breathing in asthma, chronic cough, bronchitis, bronchiectasis and mucoviscoidosis. (The physiologic *basis for intermittent positive pressure breathing* in children is schematically outlined in FIGURE 17.)

Aerosols

The aerosols administered jointly with inspiratory intermittent positive pressure breathing are usually of four types, (1) bronchodilators, (2) antibiotics, (3) detergents, or wetting agents, anti-foam solutions, and (4) digestive enzymes The most satisfactory bronchodilator in children has been Isuprel (isopropylarterenol). Vaponefrin (a racemic epinephrine solu*tion) has been used in those patients initially* or eventually nonresponsive to Isuprel. Among the antibiotics, terramycin, penicillin, streptomycin, albamycin and erythrocin have been used when organisms were shown to be sensitive to that particular drug. Alevaire was used initially as a wetting agent to help in the reduction of surface tension, liquefaction and emulsification of mucus and potentiation of [illegible] solution containing superinone, glycerine, potassium bicarbonate and silicone, has been found to be very satisfactory. The enzymatic agents, Tryptar and pancreatic dornase are used sparingly when indicated for further *liquefaction* of thick, tenacious *secretions* in children with asthma, bronchiectasis and mucoviscoidosis.

Bronchial Hygiene and Other Supportive Measures

General measures concerning diet, clothing, fatigue, environment, irritants and immediate treatment of respiratory infections, must be included in a respiratory therapeutic regimen. Gamma globulin may be helpful in those children with hypogammaglobulinemia, associated with chronic respiratory conditions. There is a place for the use of steroids in *asthmatic* children during acute stages Occasionally, the combination of a tranquilizer and a steroid, such as ataraxoid, may be of considerable value Bronchial hygiene, including bronchoscopy, has proven to be life-saving many times. Physiotherapy and breathing exercises can be of considerable benefit in older children; psychotherapy often contributes greatly in those cases with an emotional background.

With the better understanding of bronchopulmonary diseases in infants and children will come earlier diagnosis and treatment. Not only will lives be saved, but the progression to

* Defomair supplied by Winthrop Laboratories on an experimental *basis*

chronic respiratory invalidism at a later age may be prevented.

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Bronchial Asthma: Pathophysiology, Pulmonary Function Tests and Therapeutic Aspects

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BRONCHIAL asthma is a distressing and common form of acute, recurrent or chronic bronchial inflammation and obstructive emphysema, usually of allergic origin. The acute paroxysm of bronchial asthma may last for minutes to hours or recur in varying degrees of severity for days. Finally, a state of intractable asthma, during which the episode is continuous and refractory to treatment, may result. In this state, the patient presents a picture of marked physiologic imbalance. Evidence of hypoxia, cyanosis, dehydration, disturbed psyche, peripheral vascular collapse and further disturbances may be noted because of changes induced by the widespread use of drug therapy. Death is most commonly the result of asphyxia, resulting from the plugged and obliterated bronchi and bronchioles. Other causes of death include oversedation; the failure of endogenous discharge of adrenal hormones (necessary in the defense mechanism against stress), and in more recent years, to steroid sequelae.

PATHOPHYSIOLOGY

Bronchospasm is the basic functional disturbance in chronic bronchial asthma. Obstruction of the airways interferes first with the ventilatory function. Allergen-antibody reactions on the cell surface provide potent stimuli for the various cells, which respond by contraction (smooth muscle), secretion (glands), change in tonus and permeability (capillaries). Furthermore, the release of biologically active substances such as histamine, acetylcholine (and possibly serotonin) by the disturbed cells induce local and general changes in a hypersensitive organism which frequently exceed physiologic limits and lead to functional and structural disturbances.

Bronchial obstruction from any cause interferes with the movement of air in and out of the lungs, requiring much greater force for a given ventilatory volume. Both the elastic and the flow resistance of the lung are greatly increased. As a consequence, the lungs appear stiffer, i.e., the pulmonary compliance is lower than normal. The mechanical resistance to airflow, of course, is decidedly augmented. Thus, the energy requirements for the breathing process rise considerably.

FIGURE 1A–D demonstrates the mechanics of breathing in a normal subject, a patient with chronic bronchial asthma (bronchospasm produced by the subcutaneous injection of 0.1 mg. Mecholyl) and a patient with chronic pulmonary emphysema. It will be seen (FIG. 1A) that both types of patients require considerably greater transpulmonary pressure differences for a given tidal volume, produce much lower airflow rates and need proportionately more time for expiration than does the normal subject. During normal breathing at a respiratory rate of 15 to 17 per minute, the values for compliance were as follows: .111 L./cm H_2O for the normal subject, .117 L./cm H_2O for the patient with chronic bronchial asthma and .054 L./cm.H_2O for the patient with chronic pulmonary emphysema. The values for mean resistance to inspiratory airflow (FIG. 1C) were 1.7; 15.0 and 24 cm.H_2O/L./second respec-

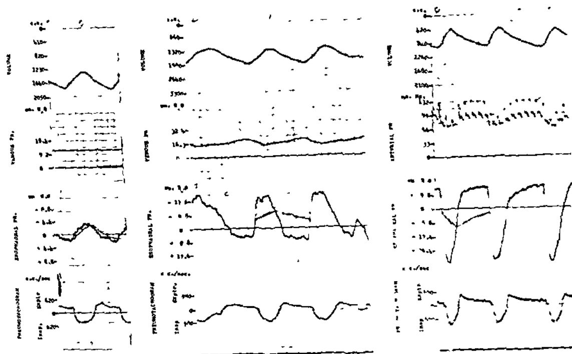


FIG 1 —(A) Ventilatory dynamics in supine position during quiet breathing in (*left*) a normal patient (C B , male, 37 yr), (*center*) a patient with chronic bronchial asthma during induced bronchoconstriction (C M , male, 21 yr), and (*right*) a patient with severe chronic pulmonary emphysema (W L , male, 49 yr)

tively. As a consequence, the loops formed by a pressure-volume plot (FIG 1B) are much wider for the 2 patients than for the normal subject

The expiratory phase requires active work for the patient with bronchospasm, in the normal subject, expiration is passive The widening of the pressure-volume loop in the two patients indicates that the largest part of respiratory work is expended in overcoming the mechanical resistance to airflow. In addition to the marked increase in inspiratory resistance (FIG 1C), the pressure-flow relationships are characterized by the formation of a loop during expiration, indicating that the pressure necessary to obtain a given flow increases progressively over the expiratory cycle This is caused in part by the progressive narrowing of the airways as deflation proceeds, and possibly also in part by "ball-valving" during expiration The disproportionate increase in expiratory airflow resistance, associated with a prolongation of the expiratory time is demonstrated in the 2 patients as compared with the normal subject (FIG 1D) in a plot of resistance changes over the entire respiratory cycle

These changes in the physical properties of the lung produce a number of further alterations in the cardiopulmonary function of the asthma patient If the expiratory forces are insufficient to expel all of the inspired air against the increased airway resistance, air will be trapped in the lungs The latter become overdistended (acute or chronic pulmonary emphysema) and the midposition of the lung rises. At the same time, the diaphragm is displaced caudally and its movements become less efficient Overinflation of the lungs, within certain limits, puts the expiratory muscles in a better position to perform additional expiratory work and tends to increase the diameter of the airways However, because of bronchial occlusion in various lung segments (bronchospasm, redundant mucosal folds, secretions, etc), part of the lung no longer takes part in the actual alveolocapillary gas exchange The reduction of the vital capacity observed in patients with chronic bronchial asthma is primarily due to a decrease in the ventilated lung volume. This is

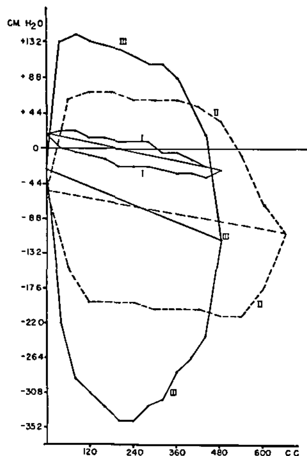


Fig 1 —(B) Pressure-volume relationship during quiet breathing in normal patient (I), in patient with chronic bronchial asthma, during induced bronchoconstriction (II), and patient with long-standing, severe chronic pulmonary emphysema (III) (supine position).

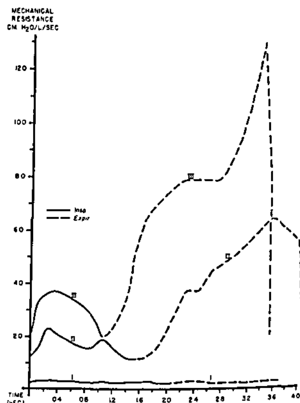
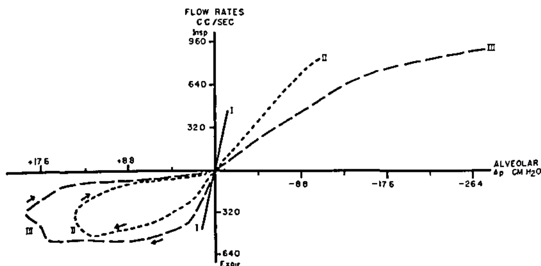


Fig 1 —(D) Mechanical resistance-time relationship in different patients in supine position during quiet breathing (I) Normal, (II) chronic bronchial asthma and (III) chronic pulmonary emphysema



[illegible] (I), patient
ig-

TABLE 1—*Relationship Between the Duration of Asthma and Increased Residual Volume*

Duration of Asthma (yr)	(RV/TLC) × 100	TLC (% of Predicted)	
		Average	Range
5	43 0	112 3	93 6–130 6
6–10	43 2	120 0	108 3–131 3
11–20	48 8	130 0	110 8–185 0
20	50.2	134.6	110 0–176 5

particularly evident if one compares a fast (forced) vital capacity against a slow vital capacity. In the first instance, the initially high expiratory flow rates tend to increase bronchial obstruction, thus preventing part of the air from being expelled A slow expiratory effort on the other hand, associated, of course, with lower airflow rates and lower pressure gradients, has a less detrimental effect on the geometry of the airways, thus allowing a larger expiratory volume

The longer chronic bronchial asthma has been present, the more marked becomes the over-inflation of the lung (TABLE 1). Bronchial obstruction, of course, is associated with unequal ventilation Thus, certain areas of the lungs are overventilated, while others take no or little part in the ventilatory process. This leads to a defective gas exchange across the alveolocapillary membrane. Because overventilated alveoli cannot compensate for the reduction of the oxygen exchange in the underventilated alveoli, the oxygen saturation of the arterial blood decreases. Owing to its greater diffusibility, the transfer of carbon dioxide is less affected. Thus, the disturbance of the ventilation-perfusion ratio resulting from unequal ventilation leads first to hypoxemia and only considerably later, when complicated by diffuse obstructive emphysema, to carbon dioxide retention and respiratory acidosis. This picture may be accentuated because unequal distribution of gases is usually associated with unequal perfusion. The latter may easily occur in the wake of local intrapulmonary pressure differences associated with uneven ventilation. With the decrease in the effective alveolocapillary surface, the diffusing capacity of the lung may be decreased. The changes in pulmonary circulation are characterized by an increase in pulmonary artery pressure and pulmonary vascular resistance and a decrease in

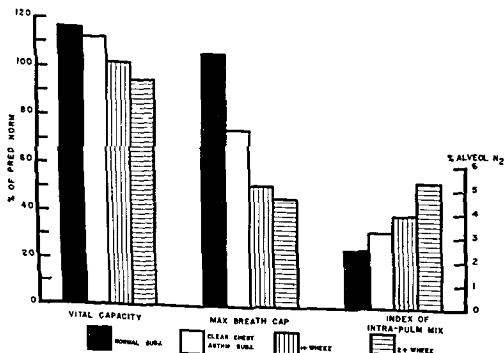


FIG 2—Correlation between lung findings (wheezing) and such tests as vital capacity, maximum breathing capacity and intrapulmonary mixing.

cardiac output during bronchospasm. The increased work load both for the respiratory and cardiac muscles will eventually lead to cardiopulmonary failure during the evolution of the disease.

Because of the cyclic variations in the disease, the state of pulmonary function changes rapidly. However, even in the symptom-free stage, the asthma patient usually shows a somewhat lower level of over-all pulmonary function, as

TABLE 2.—*Cardiopulmonary Function in Chronic Bronchial Asthma**

	Normal	Symptom free State	Broncho-spasm	Post Treatment	Reference
Lung Volumes					
V.C.	♂ 27.63-(.112 × age) × ht	3.3	2.5	—	Gaensler[9]
	♀ 21.78-(.101 × age) × ht		3.6	3.9†	
				4.1‡	Herschfus[10]
Res. Vol.	(11.1 × ht)-1055	—	3.2	3.4†	
				2.7‡	Herschfus[10]
F.R.C.		3.1	2.4		Bates[7]
RV/TLC	20-35%		47	46†	
				43†	Herschfus[10]
Ventilation					
M.B.C.	♂ 86.5-(.522 × age) × BSA	54	32		Gaensler[9]
	♀ 71.3-(.474 × age) × BSA		65	35†	
				97‡	Herschfus[10]
1st sec/TVC %	83%	58	59	54	Dulfano[8]
Mixing % N_2	<2.5%		4.2	2.2†	
				3.0‡	Herschfus[10]
"efficiency %	57	35	28		Bates[7]
Dead Space/TV	25-30%	28-51	40-65		Scherrer[19]
Mech. of Breathing					
Pulm. Compliance	12- 26	131	077		Attinger[1]
L./cm. H_2O	09		090		Marshall[13]
		13	040		Scherrer[19]
Insp. Resistance	1.2-2.0	6.1	18.5		Attinger[1]
cm. H_2O/L./sec		4.7		3.3	Marshall[13]
		5.8	27.0		Scherrer[19]
Exp. Resistance	1.7-2.0	9.1	25.5		Attinger[1]
		9.8	20.0		Scherrer[19]
Work of Br. Kgm./min		62	2.8		Scherrer[19]
Gas Exchange					
Art. O_2 Sat. %	97	92	84		Scherrer[19]
			87		Attinger[1]
Art. P_{CO_2} mm. Hg	40	39	42		Scherrer[19]
		40	38		Attinger[1]
CO uptake %		49	49		Bates[7]
Pulm. Circ.					
Mean Pulm. Art. Pressure	14-18	19	23	16§	Zimmerman[20]
		14	19	13†	Scherrer[19]
Pulm. Vas. Resistance dynes sec cm^{-5}	67	809	1370	842§	Zimmerman[20]
				550†	
		166	249		Scherrer[19]
Cardiac Output L./min	5.5-7.4	6.4	5.8	5.5§	Zimmerman[20]
		7.5	7.0	5.7†	Scherrer[19]

* Taken from Handbook of Respiration, 1958. Aero Medical Laboratory, WADC Technical report, 38:352

† After aminophylline

‡ After bronchodilator by aerosol

§ After adrenaline

compared to a normal individual of the same size and age; even if one considers the wide range of values encountered in normals (Fig. 2; Table 2) From Figure 2 it is apparent that the over-all reduction in ventilatory function is clearly related to the degree of wheezing Treatment, either by a nebulized bronchodilator or by parenteral aminophylline, leads to marked improvement, both in ventilatory and circulatory function (Fig. 3, Table 2). It will be seen that the ratio of the first second to the total vital capacity changes very little from the symptom-free to the bronchospastic stage and decreases in the post-treatment stage. This is due to the fact that in the latter instance, the improvement in the total vital capacity is proportionately greater than the improvement noted in the first second capacity

Pulmonary Function Tests During Chronic Bronchial Asthma

Symptom-Free State

The abnormalities of pulmonary function in this stage depend to a large degree on the duration of the disease. The vital capacity may be normal The changes in timed expiratory capacity relationships have been discussed above In long-standing disease, the maximal breathing capacity is usually decreased, while residual volume and the intrapulmonary mixing index are elevated Even if no wheezing is present, the airway resistance is usually somewhat increased No marked changes in the arterial blood gases occur Pulmonary vascular resistance is somewhat augmented

Asthmatic Attack

Both the vital capacity and maximal breathing capacity are considerably decreased This is associated with an elevation of the residual volume and the index of intrapulmonary mixing Pulmonary compliance is reduced at normal breathing frequencies and drops still further when breathing becomes more rapid. Airway resistance is greatly elevated, the rise being disproportionately large during expiration.

Hypoxemia and eventually hypercapnia develop If the bronchospasm persists long enough

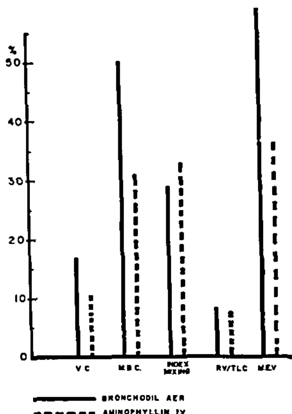


Fig 3 —Summary of improvement (per cent) of bronchial asthma after treatment by a nebulized bronchodilator or parenteral aminophylline

complicating diffuse, obstructive pulmonary emphysema follows, and respiratory acidosis may ensue. Both pulmonary artery pressure and pulmonary vascular resistance are increased in the presence of a slightly reduced cardiac output

In the spirographic tracing, the duration of the expiratory phase is increased to a much greater degree than is the inspiratory phase (Figs. 1A and 4) The expiratory spirogram shows an exponential slope in contrast to the more regular and steep slope of the normal pattern This is particularly noticeable during rapid and forced expirations, such as the forced vital capacity effort. A short initial peak flow, which may be lower than normal, is followed by very low flow rates over the rest of the expiratory phase This characteristic flow pattern shows up as a triangle on a pneumotachogram and as an exponential curve with angles on the forced expiratory spirogram (Figs. 1A and 4)

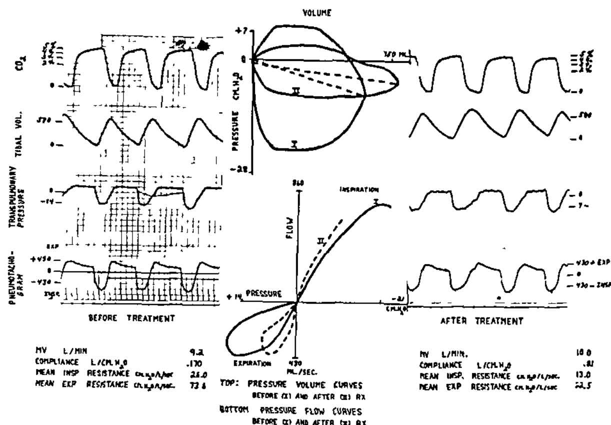


FIG 4 —Influence of bronchodilator aerosol (Nebu-Prel, 6 inhalations) on ventilatory mechanics

Bronchodilator Therapy

After treatment with nebulized bronchodilator and/or parenteral aminophyllin, an acute reversal of these changes may be observed. The forced expiratory spirogram (FIG 4) assumes a more normal pattern, while vital capacity and maximal breathing capacity increase and the index of intrapulmonary mixing decreases. Pulmonary compliance rises and airflow resistance decreases. The improvement may be such that the post-treatment tests show better values than the tests done in the symptom-free interval. However, within a short period, the pulmonary function values will again return to the level of the symptom-free interval. Both pulmonary artery pressure and pulmonary vascular resistance decrease after the administration of aminophylline, while the changes in cardiac output are insignificant. The arterial blood gas values may return to normal after aminophylline.

The pathophysiologic factors following bronchial obstruction and potentiating its effects lead eventually to the development of structural changes (loss of alveolar structure and elasticity, interstitial atrophy, progressive fibrosis and obliteration of blood vessels). Ultimately, through the continued tidal pull of the satellites (respiratory infection and bronchoconstriction), serious pulmonocardiac complications appear in the form of pulmonary hypertension, chronic cor pulmonale and electrolyte disturbances. These factors are schematically represented in FIGURE 5.

THERAPEUTIC ASPECTS

The successful management of the patient with chronic bronchial asthma requires a very careful consideration of the various responsible factors in bronchial asthma (TABLE 3).

Every attempt should be made to determine the responsible antigens. If a detailed history is inconclusive as to the cause of a patient's bronchial asthma, then scratch and intradermal testing are indicated. Removal of the offending allergen (allergic cleanliness) and a trial with specific hyposensitization should be promptly instituted in all cases whenever possible. Fur-

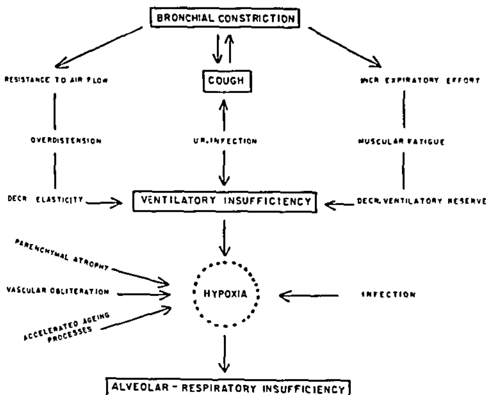


FIG 5—Development of pulmonary insufficiency from bronchial obstruction.

ther therapy should be directed towards removing the contributory factors. *Because search for the responsible agents is difficult and often completely unsuccessful, emphasis on the allergic approach to management should not exclude physiologic therapy*

Physiologic Management of Bronchial Asthma

This discussion is limited to the more important phases in the physiologic management of the patient The over-all management is outlined in TABLE 4.

Bronchiolar Relaxation

Use of epinephrine Epinephrine has been employed in various modifications, concentrations and routes Toxic reactions, intolerance and fastness are more commonly observed with over-dosage and repeated parenteral use. Deaths have been reported following intravenous administration In general, epinephrine parenterally is limited in its value to the relief of the acute attack. Unfortunately, few physicians or patients limit the dosage to the proper and effective subcutaneous injection of 0 2 to 0 3 cc. of 1:1000 dilution. We have not observed significant improvement from combinations of epinephrine 1:500 in oil.

Many patients in status asthmaticus are

TABLE 3 —*Responsible Factors in Bronchial Asthma*

Allergic
- inhalants
- contactants
- ingestants
- injectants
- miscellaneous

Paranasal sinus disease (polyposis and sinusitis)
Bronchitis (allergic or asthmatic)
Infections—common colds
Physical factors
- seasonal influences
- climatic influences
- exposure to heat, cold, drafts and abnormal humidity

Psychosomatic factors
Miscellaneous factors
- exertion
- fatigue
- endocrine
- nonspecific pulmonary irritants (tobacco, industrial and therapeutic)
- role of exertion, positional changes, laughing, shouting, crying, etc

TABLE 4 —*Over-all Physiologic Management of Patients with Bronchial Asthma*

PREVENTIVE MEASURES

Allergic cleanliness
Allergic management (hyposensitization)
Antitussive measures
Breathing re-education
Environmental controls (dust, fumes, fogs, vapors, smogs, humidity, temperature, etc)
Occupation hazards
Role of tobacco
Seasonal anti-microbial chemotherapy (preventive)
Trigger mechanisms
- chronic sinobronchitic disease
- adenoid tissue
- nasal polypi
- physical factors (temperature, humidity, laughter, shouting, etc)
- emotional factors

TREATMENT OF ACUTE ATTACKS

Adrenergic-bronchodilator aerosols (racemic epinephrine, isoproterenol, dylephrin, nebuprel-phenylephrine)
Aminophylline I V (0 25-0 5 Gm in 20 cc or 1 L D/W
Antimicrobials
Epinephrine (aqueous, gels) s c
Sedation (meperidine, paraldehyde, ether)
Tranquilizers
Hospitalization

TREATMENT OF CHRONIC (REPEATED) ATTACKS

Bronchodilator aerosols (nebulizer freon-powered or by use of continuous aerosol with air-pump or O_2 technics)
Aminophylline
- P O —(Dainites, Cardalin)
- Rectal—(solutions—technic)
- I V —(continuous flow—technic)

Antimicrobials
Iodides
Ipecac
Pressure breathing therapy (IPPB/I)
Rehabilitation
- breathing re-education
- job training

Steroids
Sedation
Surgical procedures (sympathectomy, vagectomy, resections)

TREATMENT OF STATUS ASTHMATICUS

Bronchial catharsis
Bronchscopy
Intravenous dextrose, aminophylline and sodium iodide
Oxygen
Helium-oxygen mixtures
Sedation
Steroids

epinephrine-fast, if fastness is present, the repeated use of all epinephrine preparations should be avoided until epinephrine sensitivity is restored.

Bronchodilator aerosols Aerosols of sympathomimetic drugs, such as racemic epinephrine hydrochloride, isopropylarterenol hydrochloride, 2 5 per cent racemic epinephrine and 0 5 Gm atropine SO_4 (Dylephrin), and isoproterenol SO_4, 0 4 per cent, phenylephrine HCl, 2 per cent (Nebu-Prel with Phenylephrine) have proved to be of great value for the relaxation of bronchospasm As little as approximately 0 05 to 0 10 cc nebulized by three to six compressions of a hand bulb, may abort or relieve a mild bronchospastic episode We have observed clinical and laboratory improvement with these agents (FIG 3, TABLE 2)

Recently, epinephrine and isopropylarterenol have been added to Freons in the form of a simple pocket unit (Medihaler-Epi and -Iso) designed to deliver measured aerosol dosages. The Iso unit has found popular patient acceptance and does produce improvement in timed expiratory capacity relationships in patients with mild or moderate attacks of bronchial asthma The class of Freons used to power this unit appears free of toxicity.

More recently, a Halothane-powered pocket unit has become available with an ingenious reservoir chamber with a self-cleaning, baffling device (Nebu-Halent) This device makes it possible to deliver finer, smaller particle sized aerosols of bronchodilator agents or other therapeutic aerosols as prescribed by the physician Employing Nebu-Prel with phenylephrine in this unit, we were able to determine that in mild paroxysms of bronchial asthma, 3 inhalations, and in moderately severe paroxysms, 6 inhalations, brought effective clinical relief and improvement in timed expiratory capacity relationships (FIG. 4, TABLE 5).

More severe bronchospasm may require 0 5 to 1.0 cc. of one of these bronchodilator agents nebulized continuously with oxygen or with one of the simple, portable air-pump units (N.C G.-Eliot; FIG. 6). This treatment generally requires 10 to 15 minutes at 4 L. per minute flow rate. This unit may be ideally employed for the production of continuous aerosols of all types It

requires an a c. outlet for electric power and does away with the need for the oxygen tank and regulator. The air flow rate can be adjusted by a simple turn of an air jet valve to the requirements of the therapeutic agent (rate of delivery cc. per minute). The bronchodilator aerosols may also be introduced along with intermittent positive pressure (inspiratory), thus obtaining the physiologic advantages of bronchodilation and improved alveolar ventilation. A useless cough is often converted to a productive one with this therapy.

Aminophylline (theophylline ethylenediamine). Patients vary in their tolerance to aminophylline. Some become more alert, others become drowsy; many become nauseated and even vomit, and still others complain of palpitation and sweating

Oral route For the prevention of mild but chronic attacks of bronchoconstriction, aminophylline may be given orally around the clock The addition of anti-nausea factors (local and central acting) to aminophylline has made possible the oral administration of larger, effective doses, with or without the addition of ephedrine, iodides, or a barbiturate Cardalin or the Dainite preparations are most helpful when the dose is carefully tailored for the individual patient's needs and tolerances

Rectal route. For more persistent attacks, aminophylline should be administered rectally in doses of 0 3 to 0 6 Gm (5 to 10 gr) in 15 cc. of tap water every 8 or 12 hours. For children, the dose may be reduced to 0.06 to 0.2 Gm. (1 to 3 gr.) The suppositories are not of equal value The most recent development of the disposable, small volume (2 to 4 cc.), *plastic* Rectalad unit has made possible the administration of rectal aminophylline in the simplest and yet most efficient manner This ingenious unit has been well accepted by both children and adults

Intravenous route. Intravenous aminophylline should be given for severe paroxysms of coughing or wheezing not relieved by *epinephrine* and rectal aminophylline For the attack which has persisted for less than 12 hours, 0 25 Gm (3¾ gr) in 10 cc. of distilled water usually brings prompt *relief* For the more protracted attack, the dose should be

Table 5.—(A) *Nebu-Halent—Nebu-Prel c̄ Phenylephrine Study*

No of Pts	Deg of Wheeze	Avg Impr (V C)
Avg Improvement (V C p̄ 3 Inh		
43	0	117 cc
51	+	208 cc
12	++	338 cc
4	+++	700 cc
Avg Improvement (V C) p̄ 3 Additional Inh		
43	0	52 cc
51	+	129 cc
12	++	160 cc
4	+++	344 cc
Avg Improvement (V C) p̄ Additional 1 cc Continuous Aerosols		
27	0	56 cc
28	+	56 cc.
8	++	75 cc
3	+++	150 cc

Table 5 —(B) *Nebu-Halent—Nebu-Prel c̄ Phenylephrine Study*

Summary Improvement (V C) in 110 Pts Rx c̄ Nebu-Prel—Phenylephrine

No of Pts	No of Inh	Gross Improvement
110	6	314 cc
66	additional 1 cc cont aerosols*	62 cc

* No tachycardia or side reactions observed

0.50 Gm (7½ gr.) in 200 cc distilled water. These injections may be repeated at intervals of 8 or 12 hours Syncope and peripheral vascular collapse may be observed if the rate of injection is too rapid (1 cc per minute is suggested).

For the severe acute attack of bronchial asthma occurring at home, which has failed to respond to self-administered bronchodilator aerosols, epinephrine, sedation and oral aminophylline, the following routine may be most helpful

1. Aminophylline 0 5 Gm , intravenously, in 20 cc. solution



FIG 6 —NCG-Eliot pump unit for continous aerosol therapy with plastic face mask

If the patient has not previously used adrenergic agents, the order should be reversed to Susphrine, aminophylline and meperidine The attending physician should move quietly, yet act quickly, with assurance and empathy The patient who does not respond satisfactorily in one hour's time would benefit most by prompt hospitalization

Continuous infusion technic. If intravenous aminophylline injections become necessary one or more times daily for as long as a week, the continuous infusion technic should be employed. It is advisable in most instances to add 0 5 Gm (7½ gr.) aminophylline to each liter of 5 per cent glucose in distilled water Three liters should be given in 24 hours with a flow rate of 30 drops per minute If improvement follows one or two days of such therapy, the infusions then may be given intermittently, e.g., from 9 a m to 9 p.m. daily, reducing the total to 1,500 cc. For the very sick patient, it may be necessary to continue these infusions for as long as 10 days During convalescence, rectal aminophylline should replace the intravenous

By means of pulmonary function studies we have demonstrated the presence of latent bronchoconstriction in the completely recovered state. Hence, in these patients, oral aminophylline in the form of Cardalin should replace the rectal aminophylline used during convalescence.

Pressure breathing therapy. The use of pressure breathing is based on the creation of a pressure gradient from the mouth down to the pleural space In the intermittent types the gas mixture is supplied in the inspiratory cycle, usually through a face mask (IPPB/I). There are several effective types of mask apparatus units which supply intermittent positive pressure breathing in inspiration. We have found the Bennett-type cycling valve and the new,

extremely sensitive Bird Mark 7 unit most satisfactory for administering positive pressure breathing, especially when combined with inspiratory bronchodilator aerosols. The patient completely controls the cycling of the valve by his own respiratory rhythm. An active inflation of the lungs occurs during inspiration under positive pressure from the cycling valve The rapid release of pressure at the start of expiration is followed by a high velocity expiratory gas flow (unless diffuse, unrelieved obstructive bronchial disease is present). This, combined with the release of bronchoconstriction which follows the simultaneous inhalation of bronchodilator aerosols, promotes better bronchial drainage. We employ pressures of 5 to 15 cm. of water with mixtures of air and oxygen. In general, this form of therapy should be reserved for the patient with chronic recurrent attacks who has some degree of complicating ventilatory insufficiency responsible for his disability. It is most useful in re-education of diaphragmatic breathing and preventing CO_2 retention. Striking improvement in the alveolocapillary gas exchange may be observed in hypoxic hypercapneic patients with the proper administration of this therapy

In the presence of bronchial infection, bronchiectasis or tenacious purulent secretions, the use of enzyme aerosols to attack the pus, e g , pancreatic desoxyribonuclease (Dornevac), is indicated It has proved to be efficacious in clearing bronchial infection of a chronic nature. Pancreatic desoxyribonuclease, dissolved in ½ or 1 cc of the bronchodilator aerosol, is administered by aerosol in doses of 50,000 to 100,000 units, one to three times daily for 5 to 7 days with the continuous aerosol technic or with IPPB/I It is used in addition to, not instead of [illegible]

Use [illegible]

When [illegible] the patient should be given oxygen His physical and personal requirements, as well as the concentration of oxygen desired, should be considered in selecting the type of equipment to be used Unfortunately, most patients in status asthmaticus tolerate poorly the tight-fitting rubber face masks which are necessary when concentrations of oxygen above 60 per cent are indicated. The plastic face tent, nasal catheter and a variety of lightweight comfortable plastic masks (Puritan, OEM, NCG) may produce O_2 concentrations of approximately 50 per cent in the inspired air and 40 per cent in the alveolar air at flow rates of 6 L per minute. Comfortable light plastic nasal canulae produce similar concentrations at a flow rate of 8 L. per minute.

In general, there has been an overemphasis on the danger of inducing the carbon dioxide intoxication syndrome and respiratory acidosis by the sudden administration of high concentrations of oxygen in patients with classic intractable bronchial asthma. This danger, however, is always present in patients with chronic hypoxia secondary to chronic pulmonary emphysema or chronic pulmonary heart disease particularly if respiratory depressing drugs are administered before or along with the high concentration of oxygen In these patients, the plastic nasal canulae-humidification technic is best employed. Initial low concentrations with flow rates of 1 L. per minute should be used The flow rates may be cautiously increased by daily increments to 6 L. per minute.

Most recently a new pocket device has become available providing a cooling bronchodilator aerosol with oxygen for the instantaneous relief of bronchospasm and hypoxia The Oxy-Neb* is an ingenious adaptation of the Oxy-Hale, the pocket oxygen device which delivers controlled oxygen concentrations A nebulizer is attached to the cylinder valve of the Oxy-Hale The bronchodilator solution is placed into the nebulizer. The propellant is the oxygen pressure from the pocket-sized cylinder, which is adequate for approximately 30 inhalations at the rate of 100 cc per treatment.

Helium-oxygen positive pressure breathing. If obstructive phenomena predominate, mixtures of 75 per cent helium and 25 per cent oxygen may prove more beneficial than oxygen alone Unfortunately, it is too costly for routine use Subjective relief of dyspnea and wheezing can be observed frequently following positive pressure breathing of helium-oxygen mixtures. The gas mixture may be administered through

* Oxy-Neb is manufactured by Controlled Pressures, Box 1174, Erie, Penna

the metered mask apparatus which supplies an expiratory positive pressure when the exhaled air passes through constricted orifices (NCG or OEM unit). This method may be tiring and the patient should be treated for periods of one-half to one hour four times daily. Rebreathing from the collecting bag may be permitted as an economy measure (helium-saving) The IPPB/I unit may be employed, it is most efficacious and less tiring for the patient but more costly.

Bronchial evacuation — "*catharsis*". The bronchitic cough is one of the most troublesome manifestations and may actually serve as the trigger mechanism for more extensive bronchiolar spasm

The therapeutic mechanisms for bronchial evacuation consist mainly in the use of (a) expectorants, (b) liquefaction of secretions, (c) positional drainage and (d) bronchoscopy

Expectorants. The expectorant drugs may prove quite helpful when properly used An effective productive cough should not be oversedated since mucus in the bronchioles may become tenacious and inspissated, largely from dehydration and long retention. If the mucus is permitted to become impacted, the cough may become ineffective, and a state of "tussive insufficiency" will develop One of the antihistamine preparations, diphenhydramine, combined with aminophylline may be of value, particularly in patients with associated vasomotor rhinitis Among the more ideal expectorants are the iodides, ipecac and aerosols of water, Alevaire, or the iodides (Tergital)

Iodides are excellent bronchial evacuants Their action results in dilution and liquefaction of the retained secretions. In the very sick patient 1 to 2 Gm of sodium iodide may be added to each liter of infusion fluid and continued for several days Iodides are more efficacious when the patient is well hydrated. Later, sodium iodide may be continued by oral administration. A disagreeable, metallic, bitter taste is commonly experienced The patient should be observed closely for the possible toxic complications such as skin rashes, salivary gland swelling, conjunctivitis, coryza, bronchorrhea, thyroiditis or adenopathy. Iodides should be administered cautiously. The initial dose should be 0 2 cc. of the saturated solution of potassium iodide after each meal and at bedtime This may be increased by 0.1 cc. per dose each day until a maximum dose of 1.3 cc. is reached. The dose should then be abruptly reduced to 0 2 cc and the same gradual increase of dosage repeated, this may prevent the development of intolerance. For patients in whom gastric irritation develops from a saturated solution of potassium iodide, enteric-coated tablets are available in 0 5 Gm. and 1 0 Gm. sizes.

Ipecac acts by substituting effective retching in the place of ineffective coughing Syrup of ipecac may be administered in two or three teaspoonful doses followed by a cup of lukewarm boiled water This dose may be repeated several days later, if indicated. It is always worth a trial before attempting bronchoscopy.

Liquefaction of bronchial secretions Liquefaction of tenacious secretions may be effected by nebulization of detergent aerosols, such as Alevaire, continuously for one hour, followed by a rest period of 30 minutes, another hour of aerosol, etc., until cough becomes productive of liquified secretions If necessary, this may at times be aided by an exsufflator with negative pressure (Coflator)

Positional drainage While of little benefit to those with useless cough, positional drainage may be of considerable value to the patient with accumulated secretions that are easily raised The procedure is generally most efficacious in the management of associated bronchiectasis It is more effective when carried out after bronchodilator therapy

Bronchoscopy. One of the most common and important causes of death in asthma is obstruction of the larger and smaller air passages by inspissation of tenacious secretions At times, spectacular improvement may follow bronchoscopic aspirations even in a moribund patient. Because of the danger of serious reactions to the use of Pontocaine or cocaine sprays and instillations for local anesthesia in asthmatic subjects, we generally prefer deep surgical anesthesia with ether. Intensive bronchoscopic aspiration is followed by marked subjective and objective improvement. It may prevent

atelectatic complications, prove life-saving and be followed by a long period of remission.

Antitussive measures. The most effective antitussive measures center about the prevention of various trigger mechanisms responsible for the coughing paroxysms. Laughter, shouting, talking, crying, inhalation of tobacco smoke, dusts, fumes, fogs and smogs, etc., sudden changes in temperature and humidity, and exertion are among the leading precipitating causes of troublesome coughing paroxysms.

In a recent study in our laboratory we found nonaethylene glycolmonomethyl-ether *p*-butylamino-benzoate (Tessalon) a most helpful agent in the management of pharyngitis and tracheobronchitis. Administered as an aerosol or syrup sipped slowly, this preparation has a pleasing surface anesthetic effect which, though short-lived, is free of the side reactions observed with the "caine" preparations. When this drug is administered orally in the form of perles, the antitussive effect is believed to result from action at the pulmonary parenchymal proprioceptor centers. For more sustained effects in the patient with intractable coughing paroxysms during the daytime, intensive therapy with oral narcotine (Nectadon) 30 to 60 mg. at intervals has proved quite beneficial. We have not observed respiratory depression, significant drowsiness or constipation with its repeated use. At bedtime, dihydrocodeine bitartrate, 15 to 30 mg., has been beneficial in suppressing the very severe nocturnal coughing paroxysms.

Sedation. Anxiety, fear, insecurity, restlessness, nervousness, insomnia, mood and personality deviations are commonly encountered in these patients. Accentuation of these symptoms and a frank "alert state" may be closely related to the very medications that these patients re[illegible]

gi [illegible]

ag [illegible] with a wide margin of safety used. Sodium bromide or chloral hydrate are helpful for the patient with mild, chronic recurrent attacks. When an attack has persisted for more than several hours, sedation should be given in addition to epinephrine and intravenous aminophylline.

Meperidine (Demerol), used in proper dosage, is a useful and safe drug in the treatment of the patient in an acute asthma attack or in status asthmaticus when the usual methods of treatment have failed or fastness to epinephrine or aminophylline has developed. It has a far wider range of safety than morphine. The use of meperidine for a total of two to five days, administered at intervals of six to eight hours orally or parenterally in doses of 50 to 100 mg. has not caused addiction in our patients, even when this course was repeated at intervals of several weeks. *We do not recommend its routine use in any of these patients.* Meperidine can, of course, depress respiration if given in too large a dose or if repeated too frequently in patients with chronic bronchial asthma and associated emphysema.

If meperidine is contraindicated or poorly tolerated, a retention enema of paraldehyde (20 to 30 cc.) or ether (60 to 70 cc.) may be administered at six or eight hour intervals. These have proved to be of particular value in seriously ill asthmatic patients. Unfortunately, they are often irritating and difficult to retain.

Thorazine, Compazine, Vistaril, Equanil or similar tranquilizers may be of considerable clinical value in allaying the anxieties of seriously ill patients. In the hospitalized patient, Thorazine (50 mg.) may be administered intramuscularly upon admission and at eight hour intervals for two to four days. Many patients with marked mood swings, anxiety and compulsive behavior patterns receive considerable benefit from carefully selected nontoxic tranquilizers when administered over periods of many months. The hyperkinetic reactions and mood swings which may accompany corticosteroid therapy have also been allayed in many with the simple addition of meprobamate.

Management of infection. Evidence of respiratory tract infection is present in most patients with intractable bronchial asthma. The sputum of these patients usually contains polymorphonuclear leucocytes and bacteria. There may be leucocytosis and elevation of the sedimentation rate.

In general, the choice of the antimicrobial agent depends on the predominating organisms and their drug sensitivity and the patient's tolerance for the drug. Perceptive clinical judg-

ment tempered by practical bacteriologic observation is necessary in selecting the drugs or combination of drugs and dosage to be employed in an attempt to suppress the total infection Complete eradication occurs rarely

Although the clinical activity of penicillin is entirely confined to infections caused by gram-positive microorganisms, it is the most useful of agents in these patients. Unfortunately, the high incidence of local or generalized allergic reactions to penicillin in these patients limits its use. Penicillin is of particular value for hemolytic streptococci, since these organisms are drug-sensitive Unfortunately, penicillin resistance has developed in an increasing number of strains of hemolytic staphylococci. Where such resistance is encountered, erythromycin, novobiocin, kanamycin or chloramphenicol should be administered Because of the presence of mixed gram-positive and gram-negative organisms in most of our seriously ill, hospitalized patients with intractable bronchial asthma, we frequently employ combinations of 300,000 units of procaine penicillin and 0 5 Gm streptomycin every 12 hours. These combinations should be employed only for three to seven days because of the development of streptomycin resistance in numerous instances Incidence of severe reactions to parenteral penicillin in patients with chronic bronchial asthma is higher than in the general hospital population, and a careful history of previous experiences with this drug should be elicited

As an alternative or as a primary choice, one of the broad-spectrum antimicrobial agents—oxytetracycline, chlortetracycline, tetracycline, or chloramphenicol—may be used

If, in a patient with intractable bronchial asthma, overwhelming bilateral pneumonia occurs which is nonresponsive to antimicrobial agents, the physician is justified in adding intravenous ACTH or a soluble corticosteroid preparation

Prophylactic antimicrobial therapy may be of value in debilitated patients with intractable bronchitis and asthma, who are subject to recurrent respiratory tract infections during the winter months. In general, we employ orally one of the following antibiotics: sulfadiazine 0.5 Gm, penicillin 100,000 units, or tetracycline, 100 mg., every 12 hours. These doses occasionally require slight revision.

Eradication of bronchial infection usually requires more than conversion of a purulent sputum to a mucoid one. The sputum must be adequately evacuated by employing the principles previously described of bronchial evacuation with the use of positional drainage, iodides, bronchodilator aerosols, pressure breathing therapy, bronchoscopy, etc

An irreparable sinobronchitic syndrome often follows in the wake of chronic paranasal sinus disease Free drainage of the paranasal sinuses and elimination of infection should be attempted with appropriate antimicrobial agents. The topical use of the "safer" vasoconstrictor drugs such as phenylephrine in combination with an antihistaminic, corticosteroid and antibiotic agent, is of considerable aid in maintaining nasal patency and limiting infection.

Remissive measures The use of steroid therapy *should represent but a single phase, albeit important, in the total therapeutic program* Although these hormones frequently have a striking ameliorative, anti-inflammatory and anti-allergic clinical effect (antiphlogistic), they seem only to arrest the disease, and usually do not suppress it. *They should be employed for restricted and considered use when all other conventional methods of therapy have proven ineffective in securing a remission.* Unfortunately, in the management of the patient with chronic bronchial asthma, steroid therapy may create as many problems as it solves, particularly because of the difficulty in withdrawal of the drug.

Changes noted during and subsequent to hormone therapy. The undesirable effects resulting from the clinical use of corticosteroids may be classified into two main groups: those caused by *overdosage*, and those caused by *withdrawal* of the hormone. Since successful steroid therapy depends to some degree on hormone overdosage, it is unavoidable that effective hormone therapy will be associated with some of the manifestations of overdosage. Some or all of the symptoms of Cushing's syndrome may develop, particularly diabetes mellitus, hypertension and osteoporosis. There may be some growth arrest in children Gastrointestinal

hemorrhage from activation of peptic ulcer is a fairly frequent and serious complication of steroid therapy.

Symptoms of hormone withdrawal are the result of a state of adrenal insufficiency created by hormonal suppression of adrenocortical function The symptoms may be mild or severe, depending on the dosages employed, duration of therapy and rate of withdrawal of the hormone Any additional stress in the form of trauma, shock, surgery or severe infection during this state of insufficiency may prove disastrous to the patient.

As the dose of the hormones is being reduced, aches and pains, lassitude and a wide spectrum of personality changes may occur These symptoms usually disappear when the dose is increased but may recur when another attempt is made to decrease the dose. A delicate balance must be found with each patient.

The wide variety of changes noted during and subsequent to steroid therapy are listed in Table 6

Therapeutic precautions. Among the precautions to be followed are restriction of sodium chloride in the diet to 750 mg daily while the patient is receiving ACTH, cortisone or hydrocortisone (The newer corticoid analogues do not usually require this strict restriction) The occasional use of diuretics may be helpful when indicated by the presence of hypertension and/or the excessive weight gain from fluid and salt retention Potassium may be routinely administered in the form of Pot-Amide chloride (8 tablets daily). Supplemental potassium in the form of orange or cranberry juice (8 to 12 ounces daily) is preferred by many. The supplementary ammonium chloride in the Pot-Amide preparation acts as a mild diuretic agent, and is followed by sodium and water excretion In the presence of infection or suspected infection the concomitant use of an antimicrobial is advisable In general, the patient should receive a high protein diet to offset the tendency toward negative nitrogen balance. Many physicians consider it advisable to prescribe antacids and belladonna alkaloids routinely during hormone therapy. The stool should be examined periodically for blood. Roentgenographic study of the gastrointestinal tract should be performed in all patients in whom prolonged corticosteroid therapy is contemplated Patients should receive adequate supplemental doses of corticosteroids in cases for surgery, severe trauma or other forms of major stress. To minimize adrenal suppression and atrophy in patients receiving long-term therapy with the corticoids, ACTH gel may be administered periodically as corticoid withdrawal progresses.

Use of corticosteroid hormones. Hormonal therapy should not be used until all of the lesser measures have been adequately employed. This

Table 6.—*Changes During and Subsequent to Corticotropin and Corticosteroid Therapy*

Less Serious

- Rounding of the face ("mooning"), acne, petechiae, purpura, edema, hirsutism, skin pigmentation, increased appetite, insomnia
- Headaches, aches, pains, weakness, lassitude
- Euphoria to mild depression, mental and physical hyperactivity
- Hypertension, tachycardia
- Glycosuria, hyperglycemia, aggravation of existing diabetes
- Depressed thyroid function
- Thrombophlebitis
- Sensitivity reactions (to intramuscular ACTH) skin rashes, pruritus, urticaria, occasional wheezing and angioneurotic edema

More Serious

- Potassium deficiency, muscular weakness
- Negative nitrogen balance
- Osteoporosis—fractures, especially in women after menopause and immobilized patients
- Masked infections (bacterial, viral and fungal), spread of existing infections, serious spread on non-pathogenic inhabitants of the gastrointestinal and respiratory tracts
- Mental confusion to severe psychotic manifestations, convulsions
- Exacerbation of quiescent ulcers, G I hemorrhage and perforation
- Activation and spread of unsuspected or inactive tuberculosis
- Sensitivity reaction—anaphylactic shock
- Periarteritis
- Postoperative adrenal insufficiency

Most Serious (Fatal)

- Withdrawal syndrome, "adrenocortical storm"
- Poor tolerance to trauma, shock and infection
- Active atrophy of adrenal cortices

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TABLE 6—*Changes During and Subsequent to Corticotropin and Corticosteroid Therapy*

LESS SERIOUS

Rounding of the face ("mooning"), acne, petechiae, purpura, edema, hirsutism, skin pigmentation, increased appetite, insomnia
Headaches, aches, pains, weakness, lassitude
Euphoria to mild depression, mental and physical hyperactivity
Hypertension, tachycardia
Glycosuria, hyperglycemia, aggravation of existing diabetes
Depressed thyroid function
Thrombophlebitis
Sensitivity reactions (to intramuscular ACTH) skin rashes, pruritus, urticaria, occasional wheezing and angioneurotic edema

MORE SERIOUS

Potassium deficiency, muscular weakness
Negative nitrogen balance
Osteoporosis—fractures, especially in women after menopause and immobilized patients
Masked infections (bacterial, viral and fungal), spread of existing infections, serious spread on non-pathogenic inhabitants of the gastrointestinal and respiratory tracts
Mental confusion to severe psychotic manifestations, convulsions
Exacerbation of quiescent ulcers, G I hemorrhage and perforation
Activation and spread of unsuspected or inactive tuberculosis
Sensitivity reaction—anaphylactic shock
Periarteritis
Postoperative adrenal insufficiency

MOST SERIOUS (FATAL)

Withdrawal syndrome, "adrenocortical storm"
Poor tolerance to trauma, shock and infection
Active atrophy of adrenal cortices

Use of corticosteroid hormones. Hormonal therapy should not be used until all of the lesser measures have been adequately employed. This

therapy should then be used in the lowest dosage schedule necessary to effect a remission In patients with severe seasonal (pollen) asthma, short-term therapy should be administered when the patient has failed to respond within a week to intensive antihistaminic and bronchodilator therapy started at the very outset of symptoms

Oral route We have used the following corticosteroids orally in order of their development. cortisone, hydrocortisone, prednisone, prednisolone, (Hydeltra), triamcinolone (Aristocort) and more recently, dexamethasone (16-α-methylprednisolone—Decadron)

We have observed considerable variations in individual responses to the steroids On occasion, a patient nonresponsive to prednisone or prednisolone has shown dramatic improvement with cortisone or hydrocortisone Similar observations may be noted with the newer prednisolone analogue triamcinolone (Aristocort) and dexamethasone (Decadron) In general, sodium retention and potassium depletion are much more likely to occur with cortisone and hydrocortisone than with the newer prednisone and prednisolone derivatives

During the past three years we have observed the effects of prednisolone in more than 400 adult patients with various types of chronic bronchial asthma and associated allergies The dosage schedule most commonly followed is. 5 mg four times daily for the first three days, 5 mg. three times daily for four days, 5 mg twice daily for seven days and 5 mg or less daily thereafter. Approximately 10 per cent of the patients have been able to remain on 2 5 mg. maintenance doses. Another 10 per cent have required slightly higher revisions initially and for maintenance. The majority of the patients have been maintained on 5 mg daily. During periods of unexplained stress or infections, the patients were permitted to return to their initial starting schedule followed by the same gradual reduction. Withdrawal from long-term therapy is presently advised at 1 mg. per month reduction The drug may ultimately be spaced at two or three day intervals during withdrawal Preparation for surgical procedures is accomplished by the use of either cortisone or hydrocortisone for two days before surgery, since prednisone or prednisolone derivatives do not provide full protection against stress since they have little mineral corticoid activity. Cortisone or hydrocortisone should be continued until the stress of surgery has subsided. These then may be tapered off and the prednisone or prednisolone derivative resumed.

With the use of prednisolone-meprobamate we have not observed any over-all reduction in the basic dosage requirements However, many patients with steroid-alert manifestations and those during the pollen season appear to prefer this combination. It was considered best to maintain patients with a past history of G.I bleeding on buffered prednisolone. Supplemental antacid therapy is often advisable.

We have recently reported our observations in 44 patients with chronic bronchial asthma and allied disorders who were treated with triamcinolone (Aristocort); 4 mg. of this drug was used in the therapeutic schedule in place of 5 mg of prednisolone An additional 32 patients with chronic bronchial asthma have been studied since this report There appeared to be a greater weight loss in this series than with prednisolone The over-all results were good, "mooning" and weight gain occurred in some patients but no serious sequelae were observed We have not observed any anorexia, generalized weakness or clinical evidence of excessive nitrogen or potassium loss in our patients with chronic bronchial asthma.

At the present time we have under observation 63 patients with intractable bronchial asthma being treated with dexamethasone (Decadron) with the formula, 16-α-methyl-9-α-fluoroprednisolone More than one-half of the patients have noted tremendous increase in appetite, consistent weight gain and a sense of well-being. The weight gain has been influenced but little with supplemental chlorothiazide administration However, we have noted a somewhat increased incidence of bleeding from the G I tract thus far in our observations with this drug The dosages required for suppression of intractable asthma have run in the ratio of 1:3 compared with triamcinolone Maintenance dosages of 0 5 to 0.75 mg are usually adequate for suppression of asthmatic symptoms.

I.V. route The intravenous route is the more efficacious one for the hospitalized patient in serious status asthmaticus The patient is started on a continuous infusion of 5 per cent glucose in distilled water, 30 drops per minute flow, thus ensuring approximately 3 L. per 24 hours. Aminophylline, 0.25 to 0.5 Gm., is added to each liter, depending on the patient's responses and tolerance For the patient who has not received steroid therapy quite recently, ACTH is added, 10 mg./L. and a total dose of 30 mg./24 hours is given for one to three days. Those who have been on corticosteroids should receive instead hydrocortisone or hemisuccinate prednisolone intravenously The quantitative eosinophils which are consistently elevated at the outset are usually low or absent by the second day of this program. With improvement, the ACTH is administered only in the first liter of fluid daily for several more days. In the most severe cases, the infusion of glucose and aminophylline is continued for an additional one or more days With the intravenous therapy, the immediate results are generally more striking However, the physiologic hazards, particularly disturbances in psyche, potassium imbalance and facial mooning may be more pronounced

Attempts should be made to maintain the remissive state with the use of rectal aminophylline solution or the oral Dainite or Cardalin preparations of aminophylline and bronchodilator sprays as needed During treatment and following remission, many patients note that they can "do more with considerably less" of their therapeutic armamentarium

Surgical procedures The proper management of the patient with chronic recurring bronchial asthma may tax the character and ingenuity of the physician The therapeutic problem may be made even more difficult by the family and the disturbed, emotional make-up of the patient Mutual confidence must be established between the patient and the physician. Every severe asthmatic episode should be carefully considered apart from previous seizures The "whims and cure-alls" of the patient and his family should not be curtly dismissed but discussed rationally.

Unfortunately, too often as with many chronic diseases, the hope of "surgical cures" is brought up Benefit has been described following a wide variety of surgical procedures, and, indeed, specificity has been "suggested" for these measures Notwithstanding the great technical skill of the modern thoracic surgical team, there has been little enthusiasm for those operative procedures designed to influence the neurogenic control of the bronchioles and chemical secretions Unfortunately, observations made in the laboratory on cats and dogs cannot be translated accurately into changes to be observed in humans with chronic bronchial asthma. Occasional, temporary successes have been reported following procedures attacking the sympathetic or parasympathetic (vagal) or both systems. These procedures have varied from the simpler procedures, such as procaine injection or alcohol block of the sympathetic stellate ganglia and the upper four thoracic ganglia, through a variety of unilateral and bilateral cervico-thoraco-sympatholytic or parasympatholytic designed resections Finally, bilateral resection (2 stages) of the posterior pulmonary plexus as well as resection of cervicothoracic sympathetic and complete pulmonary plexectomies have been performed Opinions differ widely as to the ideal surgical procedure for these patients Most of the early enthusiastic surgical investigators have stopped their search for surgical surcease Many patients improve temporarily after these procedures Long periods of rest in the hospital and intensive medical care may well explain this The physiologic and financial stress of major surgery, the attendant pain and discomfort, the complications of pneumothorax with ganglia surgery, trauma to bronchi and blood supply, etc., with intrathoracic procedures and the discomfort of residual unilateral or bilateral Horner's syndrome and skin temperature changes noted after sympathetic surgery are some of the disadvantages of such procedures.

Another surgical procedure has found some favor among thoracic surgeons. Beneficial results have been described in patients in whom excision of "trigger areas" of pulmonary destruction (bronchiectasis) or areas of large emphysematous bullae were carried out. Excisional surgery along with some type of

interruption of the upper sympathetic or parasympathetic vagal chain below the level of the recurrent laryngeal nerve is usually advocated by these surgeons Definite bronchiectatic disease (saccular) which is *unequivocally demonstrable* (after maximal bronchodilation) by radiography and bronchography and which has served as a nidus for recurring pneumonitis, chronic suppurative disease, pulmonary hemorrhage or progressive debility, should be treated as bronchiectasis per se and not as a possible trigger mechanism for chronic bronchial asthma The indications for resectional surgery in these patients are clearly defined and uniformly accepted. The curative results of excisional surgery for bronchiectasis are excellent. However, the course of the associated chronic bronchial asthma is usually not affected for long The segmental bronchial areas suggesting cylindrical bronchiectasis by radiography or bronchography should not be resected unless a proved saccular bronchiectatic area is present.

The authors are not encouraged by the present results of these thoracic-surgical procedures for the cure or amelioration of chronic bronchial asthma. Following surgery, these patients generally continue to require long-term intensive medical therapy Fortunately, the use of steroid therapy particularly with the newer *corticoid analogues with potentially less mineralocorticoid* reactions, intensive bronchodilation and antibiotic therapy, and physical rehabilitation have made their care more pleasant. Nevertheless, the more adequate management of this large group of "pulmonary cripples" continues to remain a challenge to the family physician and the specialist. These patients unfortunately all too frequently require an "economic prescription" and sympathetic guidance.

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Emphysema

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EMPHYSEMA is a term used to describe many different conditions, nonpulmonary as well as pulmonary. Clarification is badly needed and an entirely new set of terms would do much to aid in the understanding of the varied anatomic and physiologic disturbances which are all called by this one name. Of the 14 types of emphysema listed in the medical dictionary, we shall first eliminate all of the nonpulmonary varieties, since they are not germane to this discussion Even the term "pulmonary emphysema" refers to several conditions which differ so much in etiology, anatomy, physiology, pathology, and therefore treatment, that it is obvious that they are not the same disease entity But since the same label is affixed to all of them by roentgenologists and clinicians, a state of confusion exists wherein questions of disability, therapy and course frequently result in pointless argument and mutual doubts In an attempt to eliminate some of this confusion, we shall mention the "emphysema" diseases which will not be discussed in this chapter and the manner in which they differ from the diffuse generalized disease which is our subject.

Compensatory emphysema, sometimes called vicarious, complementary or ectatic, has no place in this discussion. It is a poor term used to describe an area of lung which is overdistended or overworking because of the collapse, inactivity or absence of other areas. Distention of lung, within an extreme limit, uncomplicated by any other change, does not interfere with normal function In fact, it is not unusual to find that a single functioning lung shows performance superior to the calculated normal level It is only when chronic bronchial or bronchopulmonary infection is present, or because of diffuse pre-existing pulmonary pathologic entities, that respiratory embarrassment occurs, with the picture of true emphysema. This explains the very great differences between patients with diseased, collapsed or removed lung areas, and subsequent compensatory emphysema. Some of them have no difficulty and live normal lives; some have minor troubles accentuated by respiratory infections; and some are respiratory cripples.

The characteristic which determines the degree of disability is not the amount of distention, unless this distention is extremely great. A lung area, distended so much that the alveoli remain larger than normal even in expiration, cannot function in a normal fashion This condition, however, is rarely seen and practically never occurs in adults. Distention seen in clinical experience is generally well within the elastic limits of the normal lung.

Compensatory emphysema is not a condition which alters the physiologic status of the lung enough to embarrass respiration. Embarrassment is due to the same conditions which produce the picture of true chronic pulmonary emphysema, and will be discussed later. It is worth noting here that the frequent respiratory difficulties following either surgery or healing in tuberculosis and surgery for lung tumor are caused, in a majority of cases, by one or both of the following factors: (1) The patients are of middle age or beyond and already have well established changes, which are associated with the development of emphysema, but under normal conditions are not sufficiently advanced to produce definite x-ray or recognizable clinical evidence and are not determinable on routine pulmonary function testing. (2) There is diffuse bronchopulmonary disease not recognizable on x-ray. This is a common experience in tuberculosis where disseminated, small calcific spots appear three to six years later in a lung that had been considered normal.

Senile or atrophic emphysema (sometimes called postural, nonobstructive emphysema)

is a clinical entity that is often confusing It is described as a part of the aging process, where loss of elasticity of lung tissues and pulmonary vessels, combined with bone and joint changes in the chest and spine, create deficiencies in pulmonary function

Studies have shown that even the appearance of a barrel chest in the senile patient is not evidence of true emphysema.[20] If the pathologic and physiologic changes of true emphysema exist, they are the result of changes occurring long before senescence and are actually a separate picture The pathologic changes of "senile emphysema" may range from the vascular and interstitial sclerosis of senescence to the more complicated picture associated with bronchiectasis, retention of bronchial secretion, or even elements of chronic hypertrophic pulmonary emphysema Any change in pulmonary function in simple uncomplicated senile emphysema is due to weakness of the muscles of respiration and the loss of elasticity of the lung parenchyma There is no obstruction, breaking down of alveoli, hyperinflation, loss of diaphragmatic action or other of the criteria of the clinical entity—emphysema It will not, therefore, be discussed in the physiology of emphysema and should rightfully be classified otherwise

Localized obstructive or bullous emphysema is a condition which is seen quite commonly, either as a separate picture or complicating true generalized emphysema It must be differentiated from congenital cysts of the lung and from cystic bronchiectasis Both of these are due to faulty development of lung parenchyma, especially to agenesis of alveoli The cysts are bronchial elements and histologically are seen to be lined with cells roughly resembling bronchial epithelium. Examination of cystic bronchiectasis may show muscle fibers surrounding the dilated areas, evidencing their origin as an embryonic fault. Clinically, the best method of differentiation is by bronchography or body section roentgenography, which shows the clear, unobstructed bronchial connection in congenital bronchiectasis and demonstrates bronchial obstruction if the shadow be a bulla

However, bronchial disease may lead to incomplete obstruction of the draining bronchi, in which case the clinical picture becomes exactly that of localized obstructive emphysema and must be so treated Differentiations can only be made when there is no complicating bronchial abnormality.

The development of emphysematous blebs and bullae depends on inflammatory changes in small bronchi and alterations in the parenchyma distal to them. The bronchial lumen is obliterated early in expiration, trapping gas in the alveoli There are probably inflammatory changes in the alveolar walls which decrease their elasticity. On expiration and during cough, positive pressure is produced, which may be as high as 100 mm Hg or more, depending on the force of expiration or cough. Normally, the alveoli compress each other in a gentle, elastic give and take process as the pressure from the chest wall and abdomen is exerted from the periphery of the lung. But when a group of alveoli have their draining bronchi obstructed, they are a comparatively solid, uncollapsible mass. They press on the contiguous alveoli which collapse further while the obstructed alveoli distend further, their walls rupture and a larger space is formed. This is the beginning of a bulla.

Dayman has shown that uncollapsed alveoli cause obstruction by pressure on bronchioles and small bronchi[12] This extends the process by involving the contiguous alveoli. The description of the process now includes the rupture of more and more alveolar walls until the bulla is formed which is seen on the x-ray. Within the bulla, pressures rise considerably above those of the normal areas resulting in pressure on bronchi and neighboring lung. This interferes with expansion of the lung and with normal ventilation through the bronchi Westermarck has demonstrated a layer of atelectatic lung circumferentially placed around these bullae This he attributes to the pressure of the bulla on the surrounding parenchyma. It is not unusual to see the bronchial tree displaced upward or to one side by such a bulla. Sometimes, when this structure is in the upper lobe, the trachea and mediastinum are pushed away from their normal midline position with the development of a typically asthmatic clinical picture Bullae have been seen to push aside the

loose areolar tissue of the anterior mediastinum and extend into the opposite chest space.

There are certain questions which remain unanswered in this study of simple distention, one-way valves and building up of high intrapulmonary pressures. First, does a bulla arise as alveolar wall after wall breaks down with the production of one large air space? The number of alveoli which would thus be destroyed would run into many thousands, leaving many bronchial openings in the bulla. This is the pathologic picture in the development of large tuberculous cavities, in which large areas of lung parenchyma break down. The cavity generally has numerous bronchial outlets. But in the bulla, a single outlet is the common finding. This suggests that some congenital structural abnormality is responsible for the bulla formation or that the destruction is in a segmental or subsegmental area that is drained by a single bronchus. The latter assumption is difficult to prove, much clinical experience being to the contrary. There is no reported anatomic evidence for the congenital nature, but an inference may be drawn from the fact that apical blebs and bullae are common occurrences, although they are seldom looked for. It is not reasonable to assume marked pressure changes and faulty bronchial drainage in the apex when none is found in the lower lobes. Thus, it has been assumed that these blebs represent congenital structures or are the results of congenital changes.

The second point to be explained is how high positive pressure develops within the bulla. It is easy to see how a one-way obstruction which is open during inspiration and closed during expiration will admit air and then entrap it. But the pressure rises in the trapped air until it is no longer less than atmospheric during inspiration, at which point no further air can enter, since gases always move from an area of a higher to that of a lower pressure. The violent changes of cough may permit air to enter once more, especially in the sharp inspiratory expansion which follows tussive effort. Thus, in a patient who coughs a great deal, a bulla may maintain a low positive pressure which, of course, rises on expiration. The picture that is difficult to explain is the large bulla which pushes lung structures and the mediastinum aside and creates enough pressure to interfere with the patency of large bronchi. It is unreasonable to assume that this is a simple building up of pressure in successive inspirations. If pressure becomes high, regardless of the mechanism, any communication with the bronchi (a region of lower pressure) will cause egress of air from the bulla, and thus decrease pressure. The increase in size and pressure must be explained by some other process.

A bulla is essentially a sphere. A slight increase in the diameter of a sphere causes a rather large increase in its volume, and thus a fall in pressure. This is what happens immediately following long drawn-out spasmodic cough or any severe cough effort. Compression has created a pressure in the parenchyma somewhere in the neighborhood of 100 mm. Hg before the expulsive phase of cough. During expulsion, there is a sudden drop of pressure as air rushes out of the bronchi. But no air rushes out of the bulla, which is blocked. Consequently, this sudden release of pressure causes a sudden rebound expansion which occurs before inspiration can begin and before similar expansion can take place in the surrounding alveoli. It is a true expansion, no matter how temporary its nature. The subsequent recoil traps the additional air, resulting in increased pressure within the bulla.

For example, if a bulla has a diameter of 6 cm., its volume, according to the formula $\frac{4}{3}\pi R^3$ (volumes of spheres), is 114 cc. An expansion of 4 mm. following cough would give a new volume of 137 cc. and a potential decrease in pressure of around 170 mm. Hg. A transient negative pressure is produced in the bulla, and air rushes in to equalize the levels, the valve being one way. Immediately after recoil, the valve shuts with 137 cc. of gas in a space which previously held 114 cc. The increase in pressure would be 170 mm. Hg if the walls were rigid. The bulla, however, expands, pressing on surrounding parenchyma until pressure relationships are equalized again. A larger bulla, approximately 6.4 cm., and further collapse of surrounding lung and bronchi are the result of this rapid change which may be repeated often in severe cough.

It is interesting to note that the pressure changes within the bulla do not have to be very high to cause collapse of the lung and distortion of the bronchial tree The lung responds to slight pressure changes, as is shown by introduction of air into the pleura Another consideration is that pressure from the bulla on contiguous parenchyma follows the laws of hydraulic pressure, gas being a fluid. Since the diameter of the obstructed bronchial lumen is a fraction of a millimeter, and the area of the wall around 113 cm , a small pressure change in the bronchus is transmitted by the walls of the bulla as a push of considerably greater force

Pressure and distortion of the bronchopulmonary units are the causes of interference in pulmonary function It is not so much the loss of lung substance, although that may be a factor if enough bullae are formed The retained air plays no part in ventilation or gas exchange and so should not be confused with the ordinary increase in residual volume in other pathologic conditions. Bullae interfere by spreading and pushing, and thereby encroaching in a physical sense on the space of functioning lung tissue.

Any distortion of bronchial or bronchopulmonary units, whether these be lobar, segmental or subsegmental, causes narrowing and diminution of the lumen of the bronchus If bronchial infection or disease is present, this may result in expiratory obstruction and the inefficient, faulty ventilation of the asthmatic type. In fact, such narrowing and interference with complete expansion of the lung invites infection and may lead to parenchymal changes with the formation of more bullae Frequently, the entire lung is involved in the disease process, with the bullae acting more as a complication than as the original disease In such cases, the disturbance of pulmonary function is many times accentuated because of the effects of pressure on already involved lungs and bronchi.

Therapy in bullous emphysema is directed to the elimination of the bulla whenever possible. This is the type of emphysema in which surgery is most often indicated and successful (see Chapter 50) However, in many cases the bullae are multiple and total resection of all involved areas is not possible Therapy should then be directed at bronchodilatation, elimination of infection and improvement in drainage. This is similar to the treatment for the bronchial component of true emphysema and will be discussed under that heading

Chronic Pulmonary Emphysema

The disease known simply as emphysema is marked by diffuse bronchial obstruction, by changes in and destruction of alveolar walls producing enlarged air sacs of varying size, by diffuse interstitial involvement, by changes in pulmonary vessels and a decrease of the capillary bed In the medical literature, it is referred to by many names, among them, hypertrophic, essential, irreversible and obstructive are the most common. Banyai has recently referred to it as "pseudohypertrophic" which is certainly a better term than the more common "hypertrophic emphysema" "Diffuse obstructive emphysema" is one of the newer popular names, but this is not a good term either since it implies that the entire condition is bronchial in nature. In truth, it is the word emphysema which is the misnomer, since that word should be used to refer to lungs or structures which are blown into or inflated, for that is the derivation of the word The condition which we are now discussing is not produced by hyperinflation, but by obstruction, destruction and tissue replacement that inhibits and prevents normal pulmonary deflation It would be much better and would terminate much confusion if we had the courage to create a new and entirely artificial name for this entity that everyone would understand

Etiology and Development

Emphysema so often follows some other chronic bronchopulmonary disease that it has been considered as a sequel rather than as an original pathologic entity This is true even in the case of so-called "idiopathic emphysema" Here, careful analysis shows long-standing bronchopulmonary disease that was thought to be clinically insignificant and unimportant.

Some of the most common preceding conditions are asthma, silicosis and other malignant pneumoconioses, tuberculosis, chronic bronchitis, and interstitial pneumonitis and fibrosis.[19] All of these have two things in com-

mon They are chronic diseases which once established continue for many years. The symptoms may come and go, but the pathologic and physiologic changes remain. Secondly, the pathologic changes include bronchial inflammation, cough, bronchospasm, parenchymal inflammatory changes and long-lasting infection.

There is some importance in the fact that these pathologic pictures are followed by emphysema primarily in males, and generally in individuals over the age of 40 We may speculate on the reasons for the relative freedom of the female from this disease, for surely asthma, chronic bronchitis and tuberculosis are found in both sexes. We may wonder why 10 years of pre-existing disease will cause emphysema when these years are in the fifth decade, but not when these years are in the second or third Hormone factors and the aging of tissues may be cited, but there is neither experimental nor clinical evidence to determine what factor or group of factors is responsible for this phenomena of age and sex.

Among predisposing factors and preceding conditions, the most constant and important is cough. This is such a commonplace occurrence and such a normal mechanism that it is hard to think of cough as a dangerous cause of irreversible pulmonary disease But the simple cough, which eliminates minor amounts of any material in the tracheobronchial tree, is a very different thing from severe spasmodic cough with bronchospasm or the inefficient, irritating cough in many chronic bronchopulmonary diseases

Normal cough has been compared to the firing of a gun which is loaded, fired and the missile expelled. In cough, the loading is a preliminary deep inspiration In the firing or powder combustion stage, the glottis is closed, and the diaphragm fixed while the muscles of the chest and abdomen compress the intrathoracic air to high positive pressure. This is almost momentary in duration, as the glottis opens and air is suddenly expelled through a narrowed bronchial tree at a high velocity and the missile (bronchial secretion or foreign matter) is expelled Here, production of pressure, narrowing of the bronchial lumen to increase air velocity and sharp expulsion of gas are the essential points in efficient normal cough These same factors, carried to an extreme by an associated disorder, are responsible for by-products and reactions that are harmful to the cardiopulmonary system.

In the normal chest, when cough is caused by a foreign body, there is never merely a single expulsive effort. The coughs tend to be multiple during one expiration Each of these is a complete cycle, lacking only an individual inspiration. Under the fluoroscope, the diaphragm is seen to rise and fix again in a series of jerky upward movements, each motion transmitting for a time a portion of the pressure developed by the muscles of the abdomen. Such a series of coughs is nature's effort to dislodge, mobilize and expel the foreign body, and it is, of course, a more efficient mechanism than a single cough would be

When constant irritation is produced not by a foreign body but by an area of inflammation or irritation, the reaction is the same. But now the offending material cannot be coughed out, since it is in the tissue of the bronchus itself. The reflex is the same and the effort becomes greater and greater Since narrowing of the bronchus is a method of increasing pressure behind foreign matter, this process goes on to a smaller and smaller lumen The chain of events leads to localized or diffuse bronchospasm with the lumen obliterated during cough Meanwhile, the force created for expulsion becomes greater and longer lasting. The clinical picture is a cough series which is almost continuous, broken only by sharp and rapid inspiration This type of spasmodic cough is inefficient because of the small volume of air that is exhaled during the sharp expulsion phase Spirographic tracings taken on a high speed drum (1,200 mm. per second) show that, while the velocity may be high, the volume is low. A higher exhaled volume is associated with a low velocity. Although the patient seems to be coughing violently, the violence is all in the effort—not in the result.

It is not difficult to determine what is occurring in the chest during such a cough spasm Pressure increases as the bronchi close down and continues to increase when the lumen is completely blocked This pressure has been

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The result is diffuse bronchial obstruction, destroyed alveoli with residual large air sacs, diffuse interstitial pathology and changes in the pulmonary circulation—the criteria of emphysema

It is apparent that irritant inhalants and dusts capable of producing fibrosis may result in emphysema. The three factors of cough, infection and bronchospasm are set up sooner or later, to act on a lung already partially inelastic, and with partial fibrous replacement of interstitial tissues The result is likely to be an accelerated change in a shorter time

Although this is a diffuse process, the onset is gradual, and development covers a period of many years It is most rapid in long-standing conditions such as extensive tuberculosis or severe asthma in which large areas or all of the bronchopulmonary system is involved at one time. In a great many cases, the pathologic changes are greatest and begin earliest in the regions where drainage is poor and where obstruction is most easily accomplished Here, the pathologic changes go on while other regions are little affected But since dilatation of alveoli brings about obstruction of contiguous bronchioles, and since destruction and distention of one lung area will interfere with bronchial drainage of the next, this process gradually spreads, involving more and more lung parenchyma

This type of development would argue the existence of early, partially advanced, and late emphysema However, emphysema, from a clinical standpoint, is always seen as an extensive disease involving most of the lung substance This is true even of cases which are examined soon after the first recognizable symptoms take place The picture is reminiscent of many another chronic disease; and we have learned that the earliest symptoms occur quite late in the course of the pathologic process.

The development of compensatory mechanisms, both anatomic and physiologic, is the explanation for this When one area or function of the lung becomes deficient, another area or function takes over. In the cardiopulmonary system, there exists normally a tremendous reserve, which is hardly touched by the conditions of ordinary living We use only a very small portion of the lung parenchyma, including the capillary bed, and a small fraction of the work potential of the muscles of respiration and the heart. When interference begins, this reserve is called on and successfully carries on routine normal function.

As the pathologic process extends in area and severity, more and more of the compensatory mechanisms are used There comes a time when exertion or disease creates a demand in excess of these functions, and the first symptoms of disability appear. Because the circumstances are so unusual, these symptoms are neglected, especially since they disappear when the period of stress is over. But the process is progressive, and so is the encroachment on the respiratory reserve. A limit is finally reached when compensations break down and symptoms occur as a regular manifestation in everyday living The most common cause of physiologic breakdown is respiratory infection. The mechanism is probably inflammatory narrowing of bronchi and bronchioli and increase of secretion This additional obstruction, even when new pulmonary infiltration does not occur, is often sufficient to cause decompensation and sudden respiratory crippling

The symptoms, which now appear, are not simply those of the last change They represent all or a large part of the disorder that is present The onset, as measured by symptoms, is sudden and severe, but the disease, by this time, is well advanced and well established.

It is important to recognize this and to realize that so-called "early emphysema" is an advanced disease, and to direct treatment accordingly Neither x-ray examination nor pulmonary function testing, as it exists today, is capable of determining the presence of emphysema in its early stages The one hope of finding and perhaps arresting it lies in recognition of the existence of the pre-existing and causative factors If treatment is directed to these and to the damage that may be done, it may be possible to prevent or arrest further changes.

Pathology

The anatomic picture of emphysema is complex and varied both as to extent and the struc-

measured at levels as high as 140 mm. Hg. During the compressive phase, pressure is exerted within the entire chest and throughout all its contents During expulsion, there is a release of pressure temporarily, until the glottis closes for the next effort. But there is little release in the alveoli where air is trapped and pressure on the alveolar walls is continuous Since more air is trapped with each succeeding cough cycle, the alveolar walls distend and rupture

Associated with cough, but acting as an individual factor in the causation of emphysema, is infection Whether the bronchi were infected or not when the cough began, the chronicity, spasm and faulty bronchial drainage inevitably lead to diffuse and chronic infection. This plays its part in maintaining the cough and in producing and increasing bronchospasm and bronchial obstruction Drainage being inadequate, the infection extends deeper and deeper into the bronchial tree. In the bronchioles, the wall is so thin that the infection progresses through as well as along it Contiguous to bronchiolar walls are alveoli, and there now begins an inflammatory process in the interalveolar septa All of this is as yet on a microscopic level, and cannot be determined clinically or by x-ray Now, some alveolar walls are thickened, but, as in all inflammations, they have lost much of their elasticity

This is the key to the development of emphysema The normal alveolus has a wall of great elasticity which can withstand sudden changes in pressure of a greater magnitude than ever occur in the chest. An inflamed, thickened and inelastic alveolar wall must offer solid, almost unyielding resistance and, being unable to give, breaks. Once this has begun, if the causative factors are not removed, it must continue Since pressure is exerted according to hydraulic laws, a large sac communicating with a small bronchus will be subjected to greater total pressure than a small sac. Thus, as the walls break down and the sacs become larger, the disease progresses faster.

When an elastic alveolus has distended and the pressure is removed, it retracts to previous size But when an inelastic sac is relieved of pressure, it does not retract very much As a result of the breaking of alveolar walls and formation of large sacs, the lung becomes distended and less elastic. Another cause of inelasticity or rigidity is interstitial inflammation, whether it be in the form of early infiltration or that of late fibrous replacement Either state or any of the transitional phases interferes with elastic recoil and expansion, and again the result is a less elastic lung.

The third characteristic in this picture of developing emphysema is bronchospasm and bronchial obstruction. Normal expiratory bronchial narrowing is accentuated by inflammation, irritation or excessive vagus impulse. To this, add inflammatory thickening or edema of the mucous membrane together with varying amounts of bronchial secretion, and the resultant encroachment on the lumen of the bronchus leaves little or no free space With greater expiratory efforts, the bronchus narrows further Dyspnea or cough, therefore, may result in complete or almost complete bronchial obstruction

Bronchospasm is a common condition occurring in acute and chronic bronchitis, asthma, bronchiectasis and many other types of bronchial irritation Bronchography demonstrates this as an expiratory phenomenon in patients whose bronchi appear entirely normal in inspiration Such spasm may be linear, from one branching to another. It may be localized, appearing on the x-ray as though a string were tied around the tube It may appear as a series of localized spots in a single bronchus, giving a beaded appearance. Dilatation of bronchial elements distal to this constriction is frequently seen. It does not require much imagination to see the greater dilatation of the alveoli to which these same bronchi lead Dilated alveoli press on bronchioles, causing these to become obstructed

These three component forces working together, and one on the other, create emphysema. All three are eventually present. Their interrelated activities bring about weakening, loss of elasticity and destruction of alveolar walls, obstruction of bronchi, increasing pressure and dilatation of air spaces in the lung and gradual replacement of normal architecture by fibrous tissue.

rhythm, it is obvious that there are serious and permanent variations.

Another secondary or derived change is that of skeletal muscle. There is loss in tone and in strength As time goes on and the disease progresses, there is actual atrophy and wasting of muscles of arms, legs, back and shoulder girdle Whether this is a reflection of hypoxia (a compensatory mechanism to give the body less weight and less tissue to decrease the burden on an overburdened respiratory system) or results from decreased activity, is difficult to determine These weak, wasted muscles would cause dyspnea and fatigue on mild exertion in persons whose lungs were normal In the emphysematous patient, they represent another cause of disability

Pathologic Physiology

The changes in the physiology of respiration that are associated with and caused by the morbid anatomy of emphysema are many and varied. They involve every phase of cardiopulmonary physiology However, there is no uniformity in their production, nor is there any necessary relationship between the extent of pathology and the change in function. It is impossible to determine from x-ray appearance, or even from the gross and microscopic appearance of the lung, just which functions were most affected and the degree of pulmonary insufficiency that resulted

The various physiologic changes do not occur simultaneously There is always a progression as the disease progresses, and one mechanism after the other is interfered with Again, there is no uniformity, there is no regular chain of events that is always present There is no order that is followed in all cases Furthermore, the degree of change and the interference or loss in any one function seem to bear no necessary relationship to the degree of change, interference or loss in any other

The developing picture depends on the interrelationship of many interdependent factors There are also the many and complex methods by which one structure or function compensates for another

Changes in the function of ventilation of the lung occur early in emphysema and are found throughout the course of the disease. It should be remembered, in this regard, that the air, or more properly, gas in the lungs is not completely changed with every respiration Gas exchange goes on from that volume which is the functional residual capacity and is relatively constant, during normal ventilation, in both volume and composition. The function of ventilation is to maintain, as nearly as possible, this constancy of composition Ventilation should be easy, automatic and efficient It is true of emphysema that all three of these characteristics change. Ventilation increases in difficulty, its efficiency decreases and the patient becomes ever more aware of his troublesome breathing

The factor which first interferes with ventilation is bronchial obstruction, partial or complete, and occurring only during expiration. Contraction of bronchial musculature, edema of mucosa, secretion and inflammatory changes all play a part in this obstruction The process may be spotty or isolated during the preemphysematous period or even in the early stage of the disease, but sooner or later it is a diffuse process The changes have some degree of permanence but are always increased during periods of infection

Obstruction interferes with ventilation on expiration and the interference is increased by force or speed of expiration This is in part an increase in airway resistance, but careful evaluation of expiration suggests actual blockage of large numbers of small bronchi and bronchioli The spirographic tracing may show a relatively normal appearance on quiet breathing but on rapid forced breathing (e g MBC) there is evidence of interference occurring shortly after the start of expiration and increasing throughout (Fig 1) This may, and often does, result in trapping of air within the chest so that during hyperpnea the patient may be breathing off the top of his inspiratory capacity. Studies have shown that even in the normal lung an increase in intrathoracic pressure, above a certain maximum, causes narrowing of air passages [8] In emphysematous patients, this narrowing occurred at very low intrathoracic pressures and was situated in the small airways When breathing slows down and less pressure

tures involved. In general, there are changes in the bronchial tree, lung parenchyma, pulmonary circulation, heart, diaphragm, chest cage *and in the cardiorespiratory centers of the* central nervous system Skeletal muscle is involved in a secondary way, which, by reason of its effect on cardiopulmonary function, should be considered as part of the over-all pathologic picture.

The bronchi are always involved. The mucous membrane shows the changes of chronic bronchial infection and inflammation. In many cases, edema of this membrane occurs as a diffuse or spotty affair The lining is thickened by a hyperplasia of both squamous and goblet cells. In the smaller bronchi and the bronchioles there may be peribronchial inflammation or fibrosis. Occasionally, cylindric bronchiectasis is seen. Bronchial secretion occurs in all these areas. In larger bronchi, it may line the walls, but in the smaller ones it lies in the lumen Often, the tiny bronchi are completely filled with this *material.*

The lung parenchyma is in a position of mid-distention When the chest is opened there is little if any collapse of the lungs The cut surface appears spongy and firm, and many tiny *cystlike areas are observed Occasionally,* a larger bleb occurs in one or more regions. Microscopically, few normal alveoli are seen in the advanced case. The spaces are composed of several or many alveoli whose walls have been destroyed, forming larger sacs *These walls may* appear thin, but many of them are thickened by interstitial exudates or fibrosis Most of the elastic tissue has been destroyed Areas and bands of fibrosis occur throughout the lung If tuberculosis preceded emphysema, *fibrosis,*

nodules occupy much of the lung parenchyma

The pulmonary arterioles and *capillary bed* show great changes The distended alveoli obliterate the delicate capillary network, which surrounds them, by pressure against surrounding structures. When the walls break, the capillaries have already disappeared. *Thus,* the capillary bed shows narrowing, obliteration and destruction in various areas In areas of pneumonitis and pneumonia, the channels may appear open and the area engorged. In the pulmonary arterioles, the changes range from *thickening of the walls by hyalin deposits to* sclerosis of the vessel [18] In advanced disease, especially where bullae have formed, the size of a pulmonary artery branch to a region of lung tissue is much smaller than normal.

As a direct result of the changes in lung parenchyma and pulmonary vessels, a cardiac condition develops. This is limited to the right ventricle, which undergoes strain, sometimes hypertrophy and frequently failure with dilatation.

The above changes in bronchi and lung parenchyma result in secondary changes in the diaphragm and chest cage. As the lung loses its elasticity and the bronchi their expiratory patency, there is less and less expiratory contraction. This leaves the diaphragm in a depressed position, since its active muscular contraction lowers it, and the recoil of the lung is *necessary to raise it once more The diaphragm* moves but little and eventually remains immobile As this happens, muscle atrophy occurs, as it does in all inactive muscles In long-standing emphysema, the diaphragm may appear to *be a thin membrane whose muscle structure* is not easily observed

The chest cage shows inflammatory and bone changes both in the spinal articulations and at the costochondral junctions, which results in an immobile distended rib cage

In discussing the pathology of emphysema, mention of changes in the respiratory center must be made These are not peculiar to emphysema, but rather to chronic and long-standing oxygen deficiency—hypoxia. The central nervous system has a vegatative function, as well as a physiologic one When any group of cells receives less than the necessary amount of oxygen, the vitality and sensitivity of the organ are affected This is particularly true of the brain, which is notoriously sensitive to any oxygen change. The actual physical changes in the respiratory center have not been carefully described, but from its loss of sensitivity, its failure to respond to normal stimuli and its eventual abdication as controller of respiratory

physiologic have produced a lung which responds much less to pressure changes. The parenchyma of the lung, normally sensitive to very slight changes, is now less compliant and requires a greater pressure to initiate expansion, to continue it and to perform expiratory retraction. Since airway resistance is likewise increased, it follows that the work done, even in quiet breathing must be greater in emphysema than in the normal lung. Work of respiratory muscles in the normal patient during quiet breathing is 0.4–0.6 Kg. M. per minute while in the emphysematous individual it is 5–6 Kg. M. per minute.[6]

Every factor of interference is accentuated as rate, velocity and pressures increase. The work of breathing becomes so great that it not only limits the respiratory response to need, but the oxygen cost becomes so great that it produces an oxygen debt increasing faster than ventilation can liquidate it. FIGURE 2 shows the rapidly rising curve of oxygen cost of respiratory work in emphysema as compared to the more horizontal line of the *normal*. Normal healthy subjects may maintain pulmonary ventilation of 50 L. per minute at a cost of less than 50 ml. O_2 per minute. When ventilation rises to 120 L. per minute, the O_2 cost rises to over 1 ml. O_2/L. ventilation. In the emphysematous patient, the resting ventilation O_2 cost is higher and may reach 6 to 10 ml. O_2/L. ventilation at only 20 L. per minute. It should be noted that there is a critical level of pulmonary ventilation above which the respiratory muscles use all of the additional oxygen provided by the increase in ventilation, and arterial oxygen tension falls. In the young normal subject, this critical level would be about 140 L. per minute, while in the emphysematous patient it may be as low as 20 L. per minute and vary according to the extent of the disease to set a limit on ventilation and thus on exercise.[6] It may be said, for the above reasons, that dyspnea begets dyspnea in emphysema and may represent the most troublesome of all the symptoms.

One of the additional reasons for this tremendously increased work of breathing is the outward extension of the ribs toward a horizontal position. This decreases the efficiency

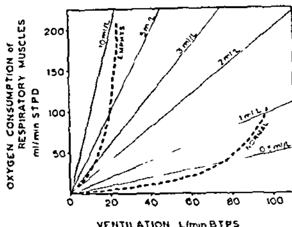


FIG. 2.—The oxygen cost of breathing. The emphysema patient has a greater oxygen cost while breathing at resting levels of ventilation. The rate of increasing cost of breathing is more striking as ventilation is increased. (From CAMPBELL, E. J. M.: Respiratory Muscles and the Mechanics of Breathing. Chicago, Yr. Bk. Pub., 1958, p. 84.)

of the respiratory muscles since the change in volume of the thorax is less for any given motion of the ribs when these approach a horizontal position as opposed to the normal downward slant.

Another major reason is the loss of diaphragmatic motion which is probably the most efficient of all respiratory movements—at least at the relatively advanced age in which emphysema is most common. The diaphragm has gradually become flattened and depressed as the lung has expanded and lost its elastic recoil. There is little, if any, motion during the phases of respiration and eventually the muscle atrophies leaving the diaphragm thin and, in extreme cases, parchment-like.

Normally the contraction of the diaphragm lowers it. In distinction to most other muscles, there is no opposing muscle so the relaxed diaphragm rises during expiration because of the elastic recoil of the lung. Both the lung and the organs of the abdomen exert force on the diaphragm. In the normal state and in the upright position, the recoil of the lung is easily able to pull up these organs along with the diaphragm. However, when the changes of emphysema have taken place, the loss of elastic recoil and the fixing of the chest in midposition leaves the diaphragm depressed, over balanced by the weight of viscera.

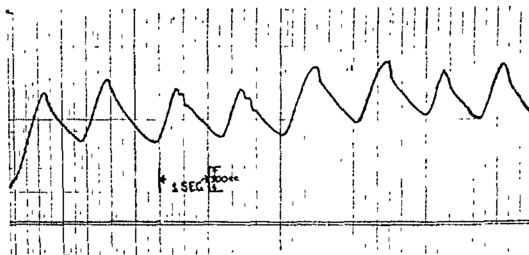


Fig 1 —Tracing during performance of MBC test Drum speed—1,200 mm per second Read left to right Rapid flow rate at beginning of expiration as demonstrated by steepness of decline soon slows with airway interference and slope becomes less steep

is used, this obstruction is gradually relieved and the curve goes back to the normal level of quiet respiration By this mechanism, ventilation loses efficiency as it becomes rapid—when it is most needed, it is least effective

Diffuse bronchial obstruction, thus hampering ventilation, has produced at the same time another physiologic defect Air trapping diminishes the expiratory reserve and increases the functional residual capacity at first temporarily and finally on a permanent basis There is now a larger air or gas volume remaining in the chest during respiration which must be ventilated by a smaller tidal air—proportionate or actual Hyperpnea results with the drawbacks mentioned above, and eventually, despite all efforts, oxygen replacement is inadequate and CO_2 is retained This change is of course reflected in the arterial blood

Meanwhile, all the anatomic pathologic changes have been developing—breaking down of alveolar walls, loss of elastic fibers, thickening of septa—so the lung remains in the semidilated position of midinspiration and cannot be retracted very much more even by the greatest expiratory effort A distortion of the ratio between residual volume and total lung capacity occurs as the former factor is now steadily increasing This is such a constant finding that the ratio RV/TLC $\times$ 100 = 35 or more is one of the classic criteria of emphysema. This is not however entirely true since average findings in people over the age of 50 will exceed that number whether or not emphysema is present Regardless of the etiology, increase in the percentage of the residual volume of air is invariably associated with poorly ventilated alveoli

The picture described thus far—bronchial obstruction, diffuse and irregular; increased airway resistance, accentuated by rate of breathing and intrathoracic pressure; air trapping with expanding functional residual capacity and residual volume—is one that is associated not only with grossly inadequate ventilation but more importantly with uneven distribution of the air Measurements of expired N_2, single breath N_2, etc (see Chapter 38) will show the extent of this uneven distribution It is noteworthy that as the disease progresses, so does the unevenness of distribution and it may be used as one of the indices of the extent of emphysema.[5]

Unequally ventilated alveoli result in unequally oxygenated capillary blood and incomplete saturation of the hemoglobin as the capillary blood is finally pooled into the pulmonary vein The ratio of poorly ventilated to well ventilated alveoli will determine how far arterial O_2 saturation will be below normal, and CO_2 elevated When respiratory infection occurs, bronchial obstruction is greater and a larger number of alveoli fall into the poorly ventilated category This is one of the reasons for the sudden deterioration of the patient's condition with such infection.

All of these changes both anatomic and

the pathologic picture suggests, and definite physiologic improvement may be secured despite the permanent and irreversible nature of the pathologic variations

The answers to the paradox of emphysema lie in the vast system of compensations which are inherent in the cardiopulmonary system. The first of these occurs during the early stages of the disease Since a very small portion of lung parenchyma is required for sedentary living, it is possible to shift function away from the involved areas to more normal ones without interfering with respiratory efficiency. There is nothing mysterious about this It is that involved lung areas have increased air flow resistance and decreased compliance and consequently, because air flow follows paths of least resistance and to regions of lower pressure, air goes into those areas in which expansion is easiest and the airways are free In a short time, the localized emphysematous area plays little or no part in respiration, and thus produces no symptoms.

As the process spreads the functional residual capacity increases. It is in this volume of air that a reasonably constant oxygen and carbon dioxide tension must be maintained. *Improved ventilation* accomplishes this by increasing either the rate or depth of breathing and eventually both Thus, more ventilation compensates for a larger volume to be ventilated *However, when exertion*, excitement, fever or any other cause increases the demand for oxygen and the need to eliminate more carbon dioxide, hyperpnea may exceed that which might be expected *both in rate and in* duration But this is occurring at a time in life when breathlessness after exertion is expected and its excess may not be noticed for a long time. It is probably true, on the other hand, that this same hyperpnea is accelerating the pace of the development of emphysema

Even when the disease is well *established*, compensatory mechanisms *continue* to work Alveolar ventilation is poor and uneven. There is definite resistance to the movement of air, especially on expiration, which increases rapidly with the velocity of air movement Compliance is diminished and work of breathing made greater. Compensation for all this abnormality is difficult and *never completely* successful A type of breathing is developed which takes least effort, attempts to equalize ventilation and discount expiratory difficulties. In this, inspiration is short and quick—the noncompliant lung is not expanded much and slowly but little and quickly—since this requires less work However, this *inspiration is not* a very efficient means of alveolar ventilation, and in all probability, not too much ventilation occurs at this phase. During expiration, more can be done. The patient exhales slowly taking advantage of lowered airway resistance at this rate. He also learns to breathe against a slight expiratory pressure caused by pursed lips or narrowed glottis This accomplishes two things. The period of expiration is long enough for the gas to mix and the oxygen level is thus raised in the alveoli. Furthermore, because of the slight positive pressure, collapse of bronchioli is somewhat resisted and ventilation is made more even as air under higher pressure flows into alveoli whose pressure is now lower. It may be said that alveolar ventilation is better during expiration than inspiration This is a mechanism which takes advantage of the larger volume of functional residual capacity, in which the removal of a certain amount of oxygen changes the resultant oxygen tension less than if this volume were smaller Whatever the reason for the development of this complex compensation, conscious application of engineering principles could hardly *provide* a better one

However effective the compensation, hypoxia eventually occurs, originally with exercise and finally even at rest The lowered *oxygen* tension in the blood, stimulates the bone marrow and there is an increase in the number of red cells and also of hemoglobin. This, of course, makes it possible for a *unit volume* of blood to carry more oxygen Since it is the oxygen tension rather than the percentage of oxygen that activates this procedure, it occurs most rapidly in patients living at high altitudes. This is one compensatory mechanism which is valuable early and very disadvantageous later on when the increasing volume of red cells also increases the viscosity of the blood and adds to the burden of the heart.

The piston-like motion of the diaphragm provides a great change in intrathoracic volume with a minimum of work. A diagrammatic oversimplification of diaphragmatic action, using a piston and a chest diameter of 16 cm., shows that a 5 cm. displacement of such a piston changes the volume by about 1,000 cc. This is of course not entirely accurate, and the chest diameter at the diaphragm is always greater than 16 cm., but it indicates the large volume changes with relatively small movement of the diaphragm. When this easy effort is lost, the very much greater exertion of moving the chest cage is necessary. While the changes are going on that result in inadequate and irregular ventilation, serious damage and alteration of structure has occurred in the lung parenchyma. This alteration, discussed in Chapter 28 and also above, has left broken alveolar walls and large air sacs instead of normal alveoli. Destruction of several alveoli to form one large air sac may result in a space of the same volume, but the area of membrane in contact with the gas has been drastically reduced. If we assume an alveolus to have a diameter of 10 units (arbitrary) and a group of alveoli to have broken down to produce a sac of 30 units in diameter, the volume has been little changed, but the diffusing surface has been reduced from 8,620 to 2,925 cm.^{2}

Thus, to inadequate ventilation has been added inadequate diffusing surface. Furthermore, around this diffusing surface is the capillary network to provide gas exchange with the blood. To less surface, now must be added a smaller volume of blood in contact with alveolar air. In emphysema, bronchial and bronchiolar infection occurs at some period and generally remains as a chronic state. One of the natural developments of bronchiolitis is interstitial pneumonitis which is therefore found to some degree in all cases, although it may be considered a complication rather than a part of the emphysematous process. However, it is present, and where it exists there is hindrance to transfer of gases across the membranes (A-C block).

The composite picture is associated with a decrease in the diffusing capacity (see Chapter 39). It is impossible to determine what portion of the decrease is related to inadequate and uneven ventilation, to loss of diffusing surface, to decrease in capillary channels or to actual A-C block. The most recent work suggests that this change is one of the important and constant findings in emphysema and may play a much greater part in disability than was previously thought.

The circulatory changes are not limited to loss of capillary bed around disappearing alveoli. Expansion and pressure, within these new air sacs and bullae, narrow remaining channels. In addition, pneumonitis causes secondary changes in arteriolar walls which narrow the lumen and limit the flow. It is logical, therefore, that increased pressure in the pulmonary artery is necessary, if not at rest, certainly during and after exertion. To this may be added the increase in pulmonary artery pressure caused by hypoxemia. This added burden on the right ventricle, unaccustomed to added burdens, is another mechanism which limits activity, and the decreased circulation limiting oxygen uptake maintains oxygen debt and lengthens the period of dyspnea. Hypoxemia may stimulate increase of red blood cell formation, and the cell volume will increase. As this happens, the viscosity of the blood is elevated. The right ventricle must do more work to force this "thick" blood through capillaries and this work is tremendously increased with more rapid flow rates. The final result will be cor pulmonale (see Chapter 25).

Compensatory Mechanisms

The resultant pathologic and physiologic changes that occur in the lung during the development and course of emphysema are permanent, for the most part, and represent serious interference with respiratory function. It would be natural to expect that, from the beginning of the evolution of this irreversible disease, symptoms of pulmonary deficiency would be manifested. Such symptoms occur with small areas of pneumonia or acute atelectasis. It is characteristic of emphysema that symptoms do not occur, despite the pathologic condition, until the disease is well advanced and widespread. Even in advanced emphysema, the symptoms may be less severe than

have a true mucolytic action and are extremely valuable if they can be used with safety.

Corticosteroids and corticotropin act to reduce both the inflammation and the edema of the bronchial wall and thus make a valuable contribution to the establishment of an airway. Once the airway is established, it is better to taper off this medication rather than seek a maintenance dose, unless actual asthma exists.

The problem of the airway is one of the reasons for using intermittent positive pressure therapy It is a superior method of introducing bronchodilator aerosol and by hyperventilation starts secretion moving along the bronchi A variation of positive pressure breathing, positive pressure inspiration with high speed negative pressure expiration—exsufflation—is another valuable procedure Because of bronchospasm, the small volume and decreased velocity of cough, and the fact that interference increases with effort of expiration a high speed expiration without force or pressure on the lung, results in the elimination of secretion which is difficult if not impossible to raise by cough alone.

The second great problem is that of unequal ventilation Much of this is due to airway obstruction but some is also caused by uneven compliance of different areas of lung As the airway improves, ventilation becomes better. If intermittent positive pressure is used, not only does the airway improve faster, but there is a direct improvement in the equality of alveolar ventilation It has been shown that in this type of case, positive pressure inspiration, using air, raises the oxygen tension in the arterial blood more than normal breathing of an enriched atmosphere that raises the alveolar oxygen tension from 100 to 150 mm. Hg [19] Our own experience corroborates these findings. Intermittent positive pressure using only 30 per cent oxygen has resulted in arterial oxygen saturation in excess of 97 per cent in patients whose pretreatment saturation was from 84 to 91 per cent It seems logical to consider intermittent positive pressure treatment an important approach to the problem of unequal ventilation

Perhaps the greatest problem to the patient is inefficient breathing and the long periods of distress that follow the onset of dyspnea or hyperpnea from any cause whatever This is also one of the most difficult problems to overcome. It is important to remember that until the airway is free and functioning, to a reasonable extent at least, any attempt to improve the mechanics of breathing is unlikely to be successful But when increased ventilation is possible, the situation is changed.

It has been pointed out above that expanding and contracting the chest, in the emphysematous patient, may result in too great an oxygen cost, especially at rapid rates The diaphragm, on the other hand, aided by abdominal muscles, may carry on this work at a very much smaller cost Consequently, the motion of the diaphragm must be regained, both to regain ease of breathing and to aid the drainage of the base of the lung

There are many different methods of accomplishing this end. Pneumoperitoneum has been used [1, 14] It frees the diaphragm from the weight of the abdominal viscera and in many cases results in its normal respiratory motion being re-established Another method, one that should also be associated with pneumoperitoneum when used, is the application of a specially fitting support, which, placed below the umbilicus, tends to push the diaphragm upwards.[13] Special models, the Barach-Gordon belt in particular, are designed to allow for use and exercise of the abdominal muscles as well as elevation of the diaphragm. These supports should be used in the patient with a weak and protruding abdominal wall

If the weight of the abdominal viscera pulls the diaphragm down, then reversing the patient should push the diaphragm up. This is the basis of the "head-down" position which in practice is having the patient lie at an angle of 18 to 20 degrees [3] It has the advantage of improving drainage of the dependent bronchi while it elevates the diaphragm and improves ventilation Because the diaphragm is generally weakened and atrophic, the results are not immediate Regular treatments over varying periods may be necessary before the tone and strength of the muscle return.

A further step in this direction is to use an oscillating bed designed especially for this

During exercise or any muscle activity, oxygen is needed in increased volume to metabolize glycogen and to liquidate the oxygen debt created by anaerobic metabolism. Impaired diffusion from alveolus to hemoglobin makes increased oxygen consumption difficult, particularly because the oxygen level in the alveolus may be lower than normal. However, it is the difference between the oxygen in the alveolus and that in the capillary blood that determines the speed of diffusion. Since oxygen cannot be increased in the alveolus, oxygen in the capillary is decreased from 14 volumes per cent to 9 to 7 or even lower The difference between levels aids diffusion of oxygen and enables the muscle to receive enough oxygen, although the tissue may have to function at a lower pressure

When all of these compensations are functioning there may be extension of emphysema to major proportions before symptoms are sufficient to produce a true clinical disease The changeover generally happens with some episode of respiratory infection This increases bronchial obstruction and by so doing brings greater airway resistance, less ventilation that is even more uneven and additional work to breathing. All of the compensations break at once and the patient has an extraordinary degree of respiratory difficulty which may, and generally does, continue after the infection has gone. To the patient, this break in compensation is the beginning of his disease, although this actually had existed for a long time and was developing behind the "compensatory curtain."

Treatment

Since the anatomic changes that occur in emphysema are irreversible, for all practical purposes, therapy cannot be directed, as in many other diseases, to elimination of pathology. This is a diffuse disease and there is no diseased portion of the lung that may be removed Giant bullae may exist as a complication but truly represent another disease Surgical excision of these is of course indicated but if true emphysema remains, this must be treated separately. A surgical approach to the treatment of emphysema does exist and is discussed in Chapter 50

Therapy must be directed to the correction or improvement of whatever physiologic changes may be amenable to such treatment. It should be designed to correct reversible defects, to develop new and to extend the use of old compensatory mechanisms and by so doing to encourage the most efficient use of the existing cardiopulmonary system.

The objectives of treatment are multiple and multiple technics must be used. Although precedence of one procedure over another may exist in any particular case, the best approach is to apply these in groups of simultaneous treatments varied by each patient's picture and reaction.

The main objectives are to provide an adequate airway with as little resistance as possible, to make ventilation more even and equal, to make the work of breathing efficient and effortless, and to remove some portion of the burden on the right ventricle.

The establishment of an adequate airway is itself a multiple project Infection, which is always present, must be eliminated. Any of the antibiotics will probably be effective, but should be used for a longer period than is customary in a less chronic case Bronchodilators are likewise essential These may be given by aerosol and systemically at the same time

Another interference with the airway is the ever present bronchial secretion and free drainage must be established. Adequate aerosol therapy is helpful, often making it possible for the patient to cough and expectorate sputum with much less effort. Detergent aerosols seem to be of greater value than water or normal saline, probably because they aid the penetration of water into mucus and because, by lowering surface tension, the droplets spread out, wetting a larger area of bronchial mucosa The wetter the mucosa, the more likely mucous secretion will continue up and along the bronchi and trachea towards expectoration. The addition of propylene glycol to such an aerosol solution decreases the spread of droplets so a detergent aerosol which does not contain it gives better results Actual liquefaction of secretion is best secured by a high fluid intake plus potassium iodide. Aerosols of enzymes

of the alveoli. The improvement in the patient at this point will be remarkable unless he is one of the cases in which marked changes have occurred in the structures of the alveolar wall producing varying degrees of alveolar capillary block Clinically, there is some A-C block in all emphysema, but in the majority of cases it is not sufficient nor sufficiently widespread to be noticed or even measured.

When A-C block is present, there is little that can be done in the way of direct therapy. Corticosteroids are used, but there is no evidence that any measurable change in the alveolar wall has taken place. Any improvement is more likely due to the effect on the bronchi with subsequent increased ventilation There is some suggestion that specific proteolytic enzymes might be of some value here, but as yet there is no experimental or clinical work that is conclusive.

There is the other reason for failure of oxygen utilization, and that is failure of pulmonary circulation These are the cases in which extensive changes occur in the vascular bed. Narrowing of pulmonary arterioles caused either by pathology of the vessels or by the surrounding inflammatory process increases pulmonary artery pressure at rest and causes a rapid rise with even moderate exercise The cardiac output is generally somewhat increased at rest The unyielding vascular bed and the increase in expiratory pressure with exercise, bring about extensive elevations in pressure with slight increments in volume and rate of flow The result is a very slight increase in cardiac output associated with exercise and a similar slight increase in oxygen consumption despite dyspnea This can be differentiated from A-C block by administration of oxygen. In the latter condition, oxygen consumption increases immediately, while in circulatory failure the change is little and delayed Treatment of the pulmonary and cardiac condition is of course necessary in this type of emphysematous patient (see Chapter 25).

In a discussion of the physiologic basis of therapy in emphysema, one more avenue of approach must be mentioned—physical activity and the state of the skeletal muscles. As stated above, the emphysematous patient has gradually developed into a state of inactivity with loss of muscle tone or even wasting of skeletal muscles. It is important to bring these muscles back to a state of relative efficiency and strength so that mild exercise will not produce dyspnea. This should be begun early with a program of slow walking on a level surface. Even this is too much for most patients producing a rapidly developing oxygen debt, dyspnea and weakness. As a result, exercise is often delayed. To overcome this problem, the addition of small volumes of oxygen to the inspired air is needed. This can be done using a long plastic tubing with either a plastic mask or nasal cannula or catheter, connected with an oxygen source. A more flexible method is the use of light weight, self-contained oxygen apparatuses which can be carried by the patient. One of these, which permits great flexibility in exercise programs, can be carried in the pocket and used at any stage of the exercise program, if the oxygen debt gets out of hand.* Exercise should be gradually increased with due regard for the condition and age of the particular patient. IPPB following all exercise periods aids in matching ventilation to the need created by the oxygen debt. It is worth noting that the cardiac and pulmonary circulatory status should be known before any program is begun. If activity increases the burden of the right ventricle, or if oxygen debt is not followed by a real elevation of oxygen utilization, exercise should be rigorously limited and kept within bounds of cardiac ability.

Program of Treatment

A therapy program must be translated into a practical scheme of treatment if it is to be of any value to the patient The program must be based on the physiologic problems of the particular patient and the methods that are designed to aid in correcting these particular problems. Some general rules can be delineated.

Therapy should start with antibiotics, bronchodilatation and IPPB. Antibiotics of a broad spectrum range should be given, preferably

* Oxy-Hale a small cigar-sized tube containing a small oxygen cylinder, having a valve easily operated by the patient Controlled Pressure Company, Erie, Penn.

purpose. The head may be lowered to the required angle during a cycle which requires two to three minutes. The alternation of position seems to improve drainage more than the head-down position alone, and alternating pressure and pull on the diaphragm seem to hasten its return to function

There are also several types of apparatus designed to produce rhythmic pressure on the abdomen. Some are cycled by the patient's breathing and others are independent of it Such rhythmic compression of the abdomen will no doubt prove to be very helpful if properly used

Regardless of what apparatus is used, nothing will replace muscular activity of the patient himself This should be sought in all cases, whether or not it seems feasible. When diaphragmatic motion is regained because of contraction of the diaphragm with aid in rising from compression of the abdominal muscles, the improvement is likely to be longer lasting.

Patients must be taught to use the abdominal muscles as an aid to breathing, it is not something which most people acquire naturally Ordinarily, especially when attempting to breathe deeply, the chest rises on inspiration and the abdomen is contracted—"sucked in" During expiration the chest falls and the abdomen expands Almost the exact opposite of these motions is desired to produce efficient diaphragmatic function. The chest should move but little. During inspiration the abdominal wall should move out as the diaphragm descends and the viscera require more room On expiration the muscles of the abdominal wall should contract, pushing the viscera and the diaphragm upwards. This phenomenon should be described and actually demonstrated to the patient; otherwise he will be unable to achieve the necessary co-ordination.

Instruction should *begin with the patient* lying on his back. He will not remember in which direction his abdomen should move in each phase of respiration, so we use the following fanciful but helpful suggestion: "Imagine that your belly is a balloon. When you breathe in, air goes into this balloon and it swells—your belly gets bigger. When you breathe out, the air is squeezed out of this balloon—squeeze your belly and get the air out." As an aid to this, fingers are placed over the lower costal borders and pressure upward and inward is exerted at the end of expiration This exercise should be done often and—for as long as the patient will permit at the beginning of treatment. When some proficiency is obtained, and this may require days or even weeks, the exercise may be repeated in the upright position with the patient bending forward at the waist. It is very important that the patient practice this "abdominal breathing" during his IPPB treatments, since it will be easier then and the technic will be learned in a much shorter time.

When this method has been learned, it is possible to observe the motion of the diaphragm in the fluoroscope X-rays taken in the lateral position show most clearly the change in both diaphragm and lung during the phases of respiration.

At this point, training to produce efficient breathing generally ceases. The patient is breathing well and with increased ease It should be noted, however, that such ease is present only on quiet breathing—that with hyperpnea or dyspnea, the chest will rise and the diaphragm becomes fixed, as previously. (Under stress, when the most efficient ventilation is needed, the patient drops back to the old inefficient, tiring method) To avoid this, the patient should go through a period of training with exercise and IPPB. He should be walked sufficiently to create noticeable dyspnea just before the IPPB machine is applied. Now, the therapist encourages the patient to breathe as slowly as possible and to use his abdominal muscles The IPPB apparatus will produce depth of inspiration without any effort on the part of the patient who is concentrating on his abdominal muscles and trying to prolong his inspiration A co-ordination is thus set up *which results in deeper, rather than only* faster, respiration under stress, and this keeps the abdominal muscles and the diaphragm functioning properly It is quite surprising how rapidly exercise tolerance is built up using this program

Improvement of the airway, equalizing ventilation and increasing the efficiency of breathing may result in very much better ventilation

periods of one-half hour. Deep breathing is unnecessary because the desired deposition of the aerosol is on the bronchial mucosa and the quietest respiration is greater than the volume of the dead space—150 to 200 cc.

The majority of emphysematous patients cough vigorously but, by reason of bronchial obstruction, have a very small expulsive blast. Despite constant coughing, they expectorate little of the material responsible for obstruction deep in the small bronchi. Clearing of much of this deeply retained secretion may be obtained by using exsufflation following each aerosol treatment.

With this type of therapy, improvement in the airway is noted, either by physical examination or better by change in pulmonary function testing Now, attention should be directed to the diaphragm. The exact detail will be determined by the characteristics of the particular case The patient with the large, flabby, protruding abdomen will require an abdominal support The head-down position should be used to help drain the lower lung and start diaphragmatic motion In all patients, a combination of abdominal muscle exercise plus walking and IPPB should be performed as detailed previously. None of the earlier therapy should be discontinued while diaphragmatic function is being regained Corticosteroids may be introduced early in therapy or delayed until the infection is controlled to some degree It should be remembered that peptic ulcer has been reported in 15 to 27 per cent of patients with emphysema, so these drugs should be given with adequate precaution

Although cor pulmonale may exist clinically or subclinically in many cases, no specific cardiac therapy is needed unless there is evidence of heart failure (see Chapter 25)

This is a chronic disease which will be improved but not cured All therapy must be given over long periods and gradually discontinued as the indications change Some therapy will be needed constantly

Complications

Complications are those associated with emphysema itself and those which occur because of unrelated diseases. As regards the latter, these occur usually in patients of advanced age. They may and frequently do have a variety of unrelated conditions Coronary disease, diabetes, peptic ulcer and carcinoma may produce symptoms simulating or even masking those of emphysema and must thus be evaluated and distinguished. A good pulmonary function laboratory is invaluable here.

The two major complications associated with emphysema are respiratory acidosis and infection Respiratory acidosis is discussed elsewhere (see Chapter 54). From the standpoint of treatment of emphysema, it should be remembered that it is caused by inadequate ventilation generally following a slowing of respiration Oxygen, used injudiciously, is the cause that is generally mentioned. However, in practice, the most frequent precipitating factor is narcosis or simple sedation, given to insure a good night's sleep All sedatives depress respiration and thus produce the hypoventilation needed for respiratory acidosis. Hyperventilation will eliminate sufficient volumes of carbon dioxide to change the arterial pH and bring a return toward the normal. IPPB is the simplest and safest method of securing hyperventilation in these cases.

Infection seems to be always present It is the most frequent complication and the greatest cause of pulmonary decompensation It is of utmost importance to avoid infection and to treat it rapidly once it has occurred. Protection is best secured by maintenance of a free and open airway and avoidance of retention of secretion or bronchospasm. When infection does occur, it should be treated as intensively and as completely as though it were pneumonia, which it very rapidly may become At this time, unless all symptoms disappear in 48 hours, the whole regime of treatment should be started again and discontinued only when there is sufficient evidence that function has returned to the pre-existing state.

Successful therapy in emphysema requires constant knowledge of the progressive pathology, the variations in function, and in what manner and to what degree the treatment given is affecting this pathophysiologic complex

(orally) for a minimum of two weeks and, then continued in reduced dosage for a longer time This is necessary because of the diffuse and chronic nature of the infection and the poor blood supply to many of the areas Bronchodilators should be given both by aerosol and systemically The most commonly used bronchodilator aerosols are racemic epinephrines (*e.g. Vaponefrin*), *isproteronal* (*e g*, *Isuprel*, Norisodrine) or, to avoid side reactions, isproteronal with phenylephrine (Nebu-Prel) These may be inhaled unmixed using 0.3 cc or, for a more even result, 0 5 cc of the bronchodilator mixed with normal saline or a detergent aerosol This mixture may be combined with intermittent positive pressure breathing

IPPB must be administered with care and understanding and with adequate skill in using the apparatus There are few methods which have occasioned so much discussion and so much disagreement—a great deal of which is based on differences in the skill and knowledge of the operators When used properly, it is a valuable instrument and mode of therapy When inexpertly used, it may range from ineffectiveness to fatigue and damage A few major principles should be followed

The duration of the treatment should be from 15 to 30 minutes Longer periods may be used as indicated, but less than 15 minutes is of little value in emphysema The nebulizer should be charged with 0 3 to 0 5 cc of the *bronchodilator and 2 cc of normal saline or* a detergent aerosol In addition, it is beneficial to add a heated aerosol generator in the system to provide completely humidified gas and avoid drying of the pharynx and trachea The inspiratory pressure *should* be set *between* 12 and 20 cm. water depending on the case The apparatus should be pressure sensitive and require no additional back pressure to cycle the valve. In many instances, an improperly fitting face mask, allowing leakage, will not permit a pressure rise to the predetermined point for cycling at the end of inspiration The air flow continues during expiration and the patient exhales against pressure and is rapidly fatigued. Attention to the mask or mouthpiece is as important as the apparatus.

The patient should not be allowed to take this treatment by himself. A trained therapist should stay throughout the period. Because emphysematous patients are accustomed to a rapid inspiratory phase, the therapist must constantly encourage the patient to inhale slowly There is no need of deep inspiration nor is it desirable. Constant deep breathing only tires the patient. Since the volume of inspiration *with IPPB* is *a function of time*, a slow, easy inhalation results in full inspiration without any effort on the part of the patient. Further, if the time is too short, the set pressure is reached only for a fraction of a second at the very end of inspiration, and because the column of air in the tracheobronchial tree is compressible, little or no pressure reaches the small bronchi In addition to fatigue, rapid and deep breathing may produce excess washing out of carbon dioxide The patient may become dizzy and confused This can be avoided by a pause at the end of each expiration which allows build-up of alveolar carbon dioxide. The patient rapidly learns to time these pauses to provide normal balance and his own comfort These treatments should be given three to four times a day during the first several weeks of therapy Because of early morning cough and dyspnea, the first treatment should be given soon after the patient awakes and before he gets out of bed

Associated with IPPB is therapy to aid in bronchial drainage and the opening of the airway *Liquefying medication such as potassium* iodide should be added to the basic principle of a large liquid intake The addition of fluid by aerosol is particularly valuable in emphysema It should be administered by a high *output aerosol generator. Water or normal* saline may be used, but better results are obtained from detergent aerosols These enable water to mix with the mucus more rapidly but, even when there is no noticeable change in the viscosity of the mucus, detergent aerosols make expectoration easier This is probably due to the surface tension depressant action, which causes droplets to spread over larger areas. Mucus does not adhere as easily to a wet surface and moves along the moistened mucosa with much less effort. The patient should receive this aerosol three to four times a day for

Bullous Emphysema and Pulmonary Cysts

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IN the early part of this century congenital pulmonary cysts, emphysematous blebs and bullae were considered to be most uncommon lesions. One of the first articles in the American literature devoted to this subject was presented by Koontz[24] who, in 1925, was able to collect 108 such cases from the literature Ten years later Pearson[31] reviewed the subject and included 172 reported cases. As late as 1936, Schenck[35] in his review of 233 patients remarked that two-thirds of these cases were found in foreign journals. There is some question as to the actual initial description of this type of lesion. Clagett[12] suggested that "the first report is probably that of Thomas Bartholinus, found in the Leyden edition of Malpighius in 1687" [7] It is possible that the lesion had been described earlier by Fontanus, whose description of a large air cyst communicating with the bronchi in a 3 month old infant, was referred to by Humbert[23] This latter author also noted Rokitansky's description of the autopsy report of a goose egg-size cyst in the left upper lobe of a stillborn male. Sporadic accounts were reported during the nineteenth century by Winslow,[42] Virchow,[39] Tillaux[37] and Rokitansky[32] An interesting description is presented in a book by Austin Flint,[17] in 1866

> interlobular emphysema is almost invariably traumatic, arising from rupture of the air-vesicles in consequence of violent respiratory efforts the anatomical characters consist of enlargement of the interlobular septa, the increased size being greater toward the surface of the lung, causing them to assume a wedge-like shape, and detachment of the pleura by the pressure of air beneath this membrane, producing air bladders, variable in size, and more or less numerous in a case reported by Bouillaud, there existed a sac so large that it resembled the stomach In some cases the surface of the lung is studded with numerous small elevations of the pleura, presenting an appearance compared by Rokitansky to that of froth [Fig 1] The symptoms are those incident to defective haematosis, this being proportionate to the extent to which the air-vesicles are compressed by the abnormal size of the interstitial areolar tissue Cases have been reported in which sudden death was attributed to the rapid escape of air from the cells into the areolar tissue Rupture of the pleural air-bladders may take place, giving rise to pneumothorax and collapse of the lung

The areas of confusion relative to this disease entity are emphasized by Boyd[3] in his oft-quoted statement· "It is not possible to write a satisfactory account of cysts of the lung, for the pathology is so confused and there is no correlation between the pathological and clinical picture " Cooke and Blades[13] noted "in the Armed Forces Institute of Pathology in Washington, D C, 28 synonyms under which cases of cystic disease of lung are filed " In 1948, Mooreman[29] summarized the situation with the remark "increasing knowledge has not only failed to simplify diagnosis, but it has confused rather than qualified the question of classification."

The basic purpose of this chapter will be an attempt to clarify the definitions and pathology, to suggest a useful classification, to analyze physiologic data revealed by radiology and laboratory studies, and to conclude with some brief remarks relative to the therapeutic aspects of this problem

DEFINITIONS

There are several types of cysts appearing lesions of the lung, but this chapter will be limited to a discussion of congenital cysts, emphysematous blebs and bullae Congenital cystic disease of the lung involves a developmental defect wherein pinching off of bronchial buds may occur within the lung itself. Such abnormalities may present in the form of a single or multiple cyst variously distributed within the lung substance. Unless the membrana pro-

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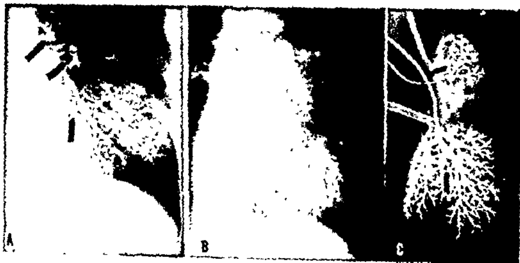


FIG 6 —Cystic bronchiectasis of left lower lobe (A) Bronchogram revealing cystic changes in superior and posterior basilar segments (B) Pulmonary angiogram (C) Postoperative injection pulmonary artery (technically incomplete filling of superior division) demonstrating normal vascular supply of cystic areas indicated by black arrows

formed a large space that often projected beyond the level of the pleura, it was situated within the lung and was covered by the intact pleura In other words, a bleb is an interstitial emphysema situated within the pleura and causes these thin-walled bladderlike prominences which are found on the surface of the lung, while a bulla is due to a vesicular emphysema situated within the lung and, though it often projects beyond the surface of the lung, is covered by an intact pleura

Unfortunately, large bullae have been referred to as cystic disease of the lung causing confusion with congenital abnormalities. One also sees other descriptive terms applied such as "vanishing lung,[11] giant air cyst, pneumatocele and bullous emphysema " Pathologic examination of bullae reveals a destruction of interalveolar septa, a variable number of communications with bronchioles and fibrotic changes both of the lesion and adjacent pulmonary tissue. These are frequently associated with pleural blebs, with varying degrees of emphysema and fibrosis of the remaining lung tissue. The bullae do not contain ciliated columnar epithelium, but are lined with the tissue resembling that of the alveolus. The loss of finer pulmonary structure may leave the bulla with a remarkably large content of smooth muscle and relatively large peripheral vascular structures

CLASSIFICATION

Two major sources of confusion are the variety of synonyms used for these lesions and the absence of a widely accepted central classification for them We believe that a truly useful classification should take cognizance of both the variable underlying histopathology and the associated pathophysiology. In order to avoid confusion, we have omitted other cavitary lesions such as those resulting from granulomatous or neoplastic processes as well as the so-called "epitheliazed cyst," a sequela of chronic lung abscess. The classification which is outlined in TABLE 1 is a direct outgrowth of the suggestions of Cooke and Blades[13] and the physiologic studies of Baldwin,[4] Kaltreider,[29] Warring[49] and Boren[3] The presence or absence of infection will alter the presenting clinical pathophysiology The type of communication with the air passages (or absence thereof) may alter the symptoms, physical findings, roentgenographic studies and particularly the pulmonary function tests The classification in TABLE 1 takes into account these several factors.

There may be some criticism of the inclusion in this classification of the transient or pseudocysts It is important, however, to remind the chest physician and surgeon that a large number of cysts may be transient. Such transi-



Fig. 4 —Extensive unilateral cystic bronchiectasis of the entire right lung occurring in a 6 year old child Lateral bronchogram shows saccular bronchi without alveolar filling

Fig 5 —Essentially universal saccular cystic bronchiectasis involving seven pulmonary segments



FIG 6—Cystic bronchiectasis of left lower lobe (A) Bronchogram revealing cystic changes in superior and posterior basilar segments (B) Pulmonary angiogram (C) Postoperative injection pulmonary artery (technically incomplete filling of superior division) demonstrating normal vascular supply of cystic areas indicated by black arrows

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TABLE 1.—*Classification of Blebs, Bullae and Congenital Cysts**

CONGENITAL PULMONARY CYSTS

- Bronchogenic Cell Type
  - Communicating with air passages
    - single or multiple
    - pulmonary sequestration
    - congenital cystic bronchiectasis
  - No communication with air passages
    - intrapulmonary or juxtopulmonary
      - single or multiple
      - pulmonary sequestration
    - extrapulmonary (intrathoracic or extrathoracic)
- Alveolar cell type
  - Communicating with air passages
    - single
    - multiple
  - No communication with air passages
    - single
    - multiple
- Bronchogenic and Alveolar Types Combined

ACQUIRED PULMONARY CYSTS

- Permanent type
  - Bullae (single or multiple) in normal lungs
    - noncommunicating
    - free communication
    - obstructive-distensive type communication
  - Blebs (single or multiple)
- Transient or pseudocysts
  - Pneumatoceles
    - postpneumonic
    - traumatic

* Modified from Cooke and Blades

ent cysts are probably more frequent than all other types of cysts combined. Recently, the term "pneumatoceles" has been applied more frequently to these transient lesions. If the term "pneumatocele" must persist, it should be amplified by using the designation, "transient pneumatocele." These lesions are primarily phenomena of infancy and childhood. However, they have been noted in association with various types of pneumonias, bronchopneumonias and aspiration pneumonitides of the adult. Initially, transient pneumatoceles were considered to be self-regulating curiosities assuming importance only if they should perforate and produce a tension pneumothorax. Watkins,[41] ourselves[1] and others noted the significant tendency of the staphylococcal pneumonias of the winter of 1957 to 1958 to produce progressive enlargement of the pneumatoceles necessitating temporary external drainage procedures. It would appear that the pneumatoceles associated with staphylococcal pneumonia of infancy represent minimal actual tissue damage but that the large cystic area results from transient or intermittent positive pressure gas forces distending areas adjacent to small and necrotic foci. Most of these lesions cause little trouble and will disappear in from two to six months. On rare occasions, they may develop a valvelike mechanism and distend progressively so as to produce a life-threatening mediastinal shift and compression. They may contain purulent exudate and perforate, thus producing tension pyopneumothorax. A transient pneumatocele should be suspected whenever a cystic lesion in a child is discovered which was not present prior to a recent penumonic episode. Two examples of interesting pseudocyst one from trauma and the other postpneumonic, with ultimate complete resolution are demonstrated in FIGURES 7 AND 8.

SYMPTOMS AND PHYSICAL FINDINGS

The symptoms of congenital pulmonary cysts appear to be dependent on (a) size, or total area of lung involvement, (b) presence or absence of infection and (c) the type of communication with the air passages. A small bronchogenic cyst without infection or bronchial communication will ordinarily produce no symptoms and most commonly is discovered on routine chest roentgenograms (FIG. 9). The rare possibility that these lesions will undergo malignant change[23] together with the unknown character of the lesion, justify surgical excision. In rare instances, extrapulmonary cysts without infection or bronchial communication may compress the esophagus and trachea (FIG. 10) or disturb cardiac function by their intrapericardial location.

When these lesions undergo infection, the symptoms may be similar to those of a lung abscess with pain, fever, purulent productive cough and hemoptysis. Congenital cystic bronchiectasis may directly imitate acquired bronchietasis. If, however, the cystic spaces are not infected, the principal symptoms will be the dyspnea of impaired pulmonary ventilation and increased respiratory effort together with

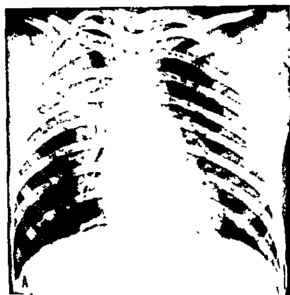



FIG 7—(A) Roentgenogram of chest soon after severe non-penetrating injury showing hemorrhagic changes right upper lobe (B) Laminogram showing extent to which hematoma of lung may imitate a solitary cyst Complete resolution occurred six weeks after injury



FIG 8—Series of chest roentgenograms demonstrating behavior of a postpneumonic pneumatocele or pseudocyst in an infant P-A view is placed directly above lateral projection roentgenogram taken on same date Pictures reveal changes occurring at two week intervals

decreased reserve due to dead space phenomena

Large air cysts which communicate freely with the bronchial pathways may produce dyspnea because of reduction of the functioning ventilatory space. In some instances, congenital lesions have been encountered in which there is a valvelike mechanism allowing for progressive distension of the large air sac. A dramatic example of this phenomenon was described in 1946 by Gross,[18] wherein he reported a successful pneumonectomy done as an emergency procedure in an infant, 3 weeks of age.

The symptoms of acquired cysts vary with

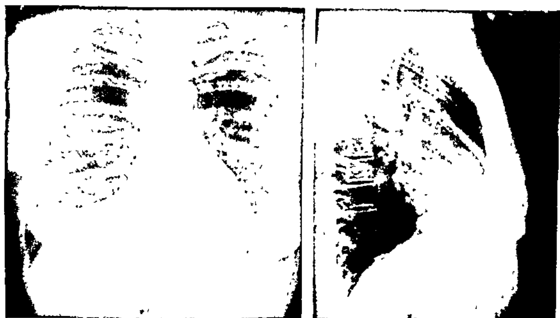


FIG 9 —Bronchogenic cyst without bronchial communication Roentgenograms reveal a solid mass of smooth contour superior and posterior to right hilar vessels

four basic features of underlying pathology (1) type of communication with air passages or pleural space, (2) conglomerate size in proportion to the thoracic contents, (3) type of associated pulmonary disease and (4) presence or absence of infection

Small bullae or blebs may be totally asymptomatic and found only as an interesting by-product of a thoracotomy performed for other reasons Excessive numbers of bullae or blebs can reduce the amount of functioning lung volume and thus produce dyspnea and increased respiratory work. Most commonly, small bullae or blebs produce distress by their rupture and resultant pneumothorax Rupture of such lesions may produce persistent pneumothorax requiring surgical intervention for its correction Large bullae, which do not communicate with the air passages or pleura, rarely give rise to symptoms Although the adjacent lung tissue is significantly compressed, a remarkable preservation of its function may occur, so that restriction of ventilatory capacity is evident only after severe stress The compression produced by such lesions may impair the ability with which adjacent lung tissue may recover from acute or chronic inflammatory episodes In large air cysts with free to-and-fro communication with the bronchi, dyspnea and decreased reserve capacity are the usual presenting complaints. The most striking symptoms are demonstrated by those lesions in which a valvelike mechanism is present at the site of communication with the air passages The production of tension within the bullae may produce localized pain of a vague or indolent type This pain may be considerably increased on effort and be falsely interpreted on initial examination as evidence of "pulmonary artery pain" as described by Harrison [19] Such lesions tend to produce cough and sometimes acute episodes of severe respiratory distress Large bullae which apparently had no communication with the bronchial tree for a prolonged period of observation, may suddenly develop evidence of an obstructive-distensive type of bronchial communication. Finally, the large bullae may become infected and develop fluid In these instances, inflammatory changes usually occur in the adjacent lung tissues. Bullae which apparently contain infected material often progress to apparent complete resolution with the aid of intensive medical measures and bronchoscopy (FIG. 11).

The physical signs produced by blebs or bullae are variable Small lesions which do not compress major vital structures usually show no abnormal physical findings Compression of the trachea or bronchi may produce a wheeze and the expected physical findings of obstruc-

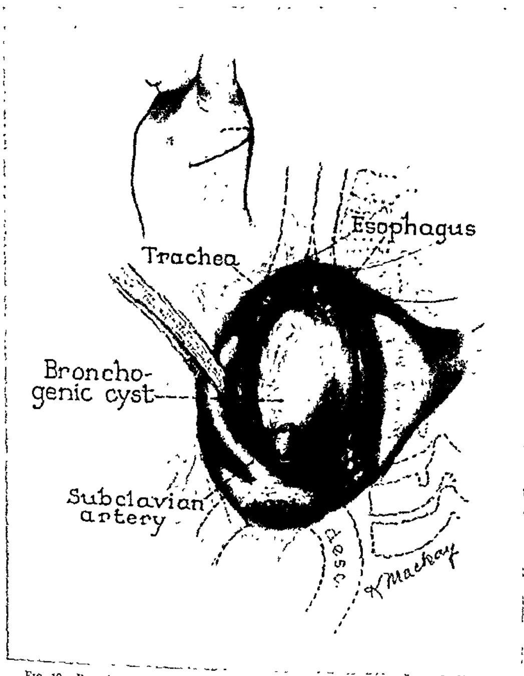


FIG 10—Bronchogenic cyst noted at roentgenography and operation to be severely compressing lower trachea and esophagus Upper inset depicts site of successful surgical incision

tive phenomena. Large air cysts compressing lung tissue may present significant broadening of Kernig's isthmus if they are located in the upper lobe areas The persistence of this broadening of the isthmus in the supine and upright position helps differentiate it from small areas of pneumothorax Compression of adjacent lung tissue may alter the breath sounds and produce atelectatic-type rales. Laennec[25] described the dry, crepitant rales with large bubbles (*rale crepitant sec a grosses bulles*); he also described a friction sound (*bruit de frottement*). Flint[17] noted that "presence of air in the alveolar structure must, of course, give rise...to exaggerated resonance of percussion...feebleness of the respiratory mur-

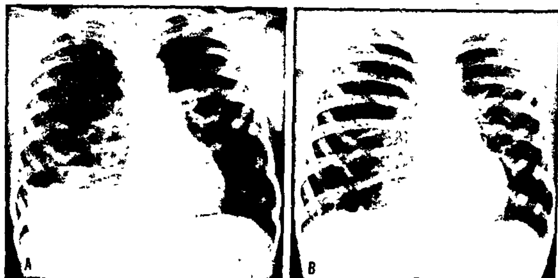


FIG 11 —P-A roentgenograms revealing (A) multiple fluid levels occurring in several bullae situated in right, middle and lower lobes and (B) clearing of fluid levels after multiple bronchoscopic aspirations and chemotherapy

mur and expansion of the lung that is restrained." We have recently described a new physical sign which we have termed "cough overtone sign"[2] which may be associated with major compression of lung tissue. This sign is a persistent localized abnormal sound heard late during the act of cough, frequently of a coarse or high-pitched nature It is believed to result from the rapid passage of air through a small or distorted lumen. It presents a sound through the stethoscope somewhat comparable to the grossly audible brassy cough of aneurysmal compression of the trachea. In many patients with bullae there is associated obstructive pulmonary emphysema with its physical findings.

Methods of Study and Physiologic Considerations

The major methods for investigation of these lesions are radiologic and physiologic

Radiologic Study Methods

In addition to the posteroanterior and lateral roentgenograms inspiration-expiration roentgenograms help define the type or absence of communication with the air passages Large congenital alveolar cysts or bullae without air communication show little or no change in size with the phases of respiration, and unless they are of considerable size, expiration may not be expected to reveal a significant increase in compression of the lung tissue adjacent to the lesion. The inspiration-expiration film must always be complemented by detailed fluoroscopic examination The degree of motion of the diaphragm, the capacity of the cyst or bulla and adjacent lung tissue to expell air, and the effect of expiration on the position of the mediastinum, all are of major significance These studies aid in evaluating whether or not there is simply cystic or bullous disease or an admixture of bullous and obstructive hypertrophic emphysema. Examples of the changes which may be found on inspiration-expiration study are shown in FIGURES 12 AND 13. Some radiologists consider laminography quite useful in lesions of this type. We believe that pulmonary angiography, although still in its developmental stages gives good promise of distinct usefulness as a diagnostic and investigative tool The technic of pulmonary angiography was used by us several years ago[3] in investigating a lung at post-mortem. There was a parallel between the extent to which obstructive hypertrophic emphysema involved areas of the lung and the characteristics of the pulmonary vascular pattern (FIG 14)

On the basis of limited studies, we believe that the circulation (both arterial and venous) of a lung-containing major bullae, particularly those with obstructive valvelike mechanisms,

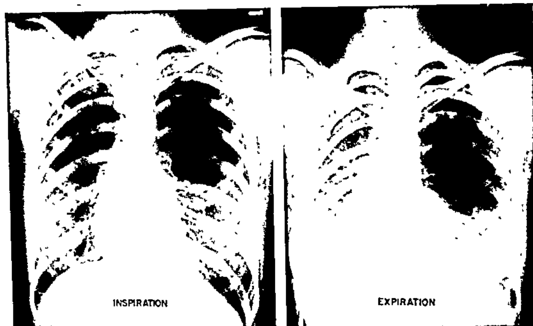


FIG. 12 —Inspiration-expiration film study of a patient with a large bulla of the left upper lobe The presence of a valvelike bronchial communication is suggested by increased size of bulla and marked mediastinal shift to the right during expiration

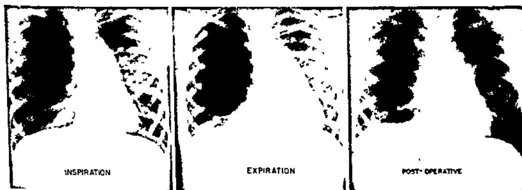


FIG 13 —Inspiration-expiration film study prior to operation suggests valvelike communication and major compression of potentially useful lung tissue Study after surgical correction reveals entire right lung had been compressed

is distinctly decreased as compared with the opposite lung Our studies,[3] as well as those of Steinberg and Robb[36] show an absence of circulation both in the area of major bullae or cysts and a decreased circulation in the tissue immediately adjacent to the lesion Angiography can be of specific help in differentiating between the markings produced by attachments of the diaphragm (FIG 15) from the roentgenographic changes produced by bullae occurring on or near the inferior surface of the low lobes. One of the most striking values of pulmonary angiography in management of emphysematous bullae is its ability to demonstrate compressed potentially functional lung tissue adjacent to the bullae, and frequently hidden by the large bullae, or by adjacent mediastinal projectures. We are extending this concept so that angiography can be utilized to help select the favorable candidate for surgery in the difficult patient group in which bullous disease is associated with moderate to far advanced obstructive pulmonary emphysema The degree of persistence and the location of the finer vascu-

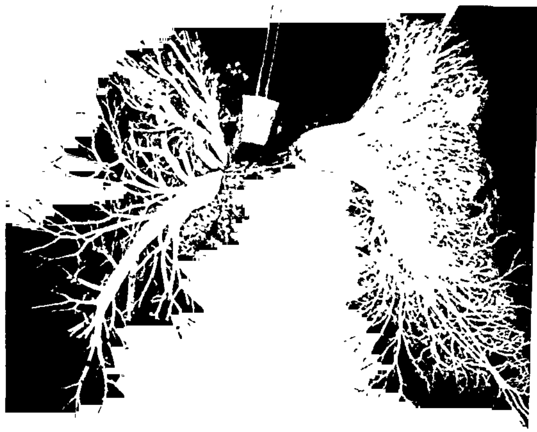


FIG 14 —Post-mortem roentgenographic study of the lungs of a 29 year old male dying with cor pulmonale Cork is situated in trachea and bronchial tree distended with air Pulmonary artery injected with barium paste Note degree of persistence of finer vascular markings paralleling decreasing extent of emphysematous distention of various lobes

lar markings is of distinct help in determining whether surgical reconstructive measures are indicated (FIG 16) Angiographic studies can also indicate the degree of hypertrophy of the right ventricle in a given situation (FIG 17) Angiographic studies before and after surgical procedures (pulmonary reconstruction, pulmonary neurectomy procedures, or combinations of the two) may be helpful in evaluating the effect of these procedures on pulmonary blood flow (FIG. 18) The finding of relatively rigid-walled structures with persistent highlights during expiration on fluoroscopy or diphasic respiratory film studies is strongly suggestive of an air cyst without bronchial communication Significant enlargement of an air cyst with coughing, the Valsalva maneuver or on expiration, frequently associated with pseudoparadoxical movement of the involved diaphragm and shift of the mediastinum, graphically illustrates the pathophysiology produced by valvelike obstructive bronchial communications. Cysts which compliantly adjust their size to the phase of respiration demonstrate free bronchial communication

Radiologic studies suggest serious disturbance in function of pulmonary lymphatics. FIGURE 19 demonstrates the lungs of an individual with far advanced, combined bullous and obstructive hypertrophic emphysema subjected to lipiodol bronchogram In this instance, the paucity of lymphatics in the peripheral lung tissues was thought to prevent removal of the dye thereby allowing persistent demonstrable opacifications eight years *after* the bronchogram. This destruction of lymphatics by overdistention of the lung was pointed out by Virchow[38] when he described "the white lung of emphysema"



FIG 15—Posteroanterior roentgenogram demonstrating a large air-cyst of right midlung field. Arrows indicate cyst and "tented" areas of right diaphragm originally misinterpreted as representing basilar bullae. Angiography and surgery proved diaphragm contour represented normal anatomical diaphragmatic attachments.

Physiological Studies

There are two basic methods of physiologic study of these abnormalities. One is the study of circulatory dynamics by means of (a) venous catheterization in the waking state and (b) its corollary study of pulmonary vascular pressures and flow by direct needle intraluminal studies at the time of open thoracotomy Data accumulated from these sources to date appear to be quite limited The other method of physiologic study consists of pulmonary function testing. This has had wider application, but further studies are needed. Many of the reports lack specific definition concerning radiologic characteristics presented by each patient investigated, particularly in regard to associated pulmonary exphysema or type of communication between the lesions and the air passages.

Pulmonary function laboratory studies. The fundamental contributions on this subject include those of Kaltreider and Fray[2] in 1939, and of Baldwin, Harden, Green, Cournand, and Richards[6] in 1950. The results of these two important communications are worthy of summary. Kaltreider and Fray reported on 6 male patients with emphysematous bullae. All had a significant degree of associated pulmonary emphysema and fibrosis, and presented a long, antecedent story of either asthma or serious exposure to industrial, irritating dust. Several of the patients demonstrated a marked reduction in total lung capacity. The vital capacity was very low in 5 of the 6 patients. The residual volume was increased in all cases, but the increment in residual volume was less than expected from comparative study of the lung size of these patients' roentgenograms with those of patients with pure diffuse obstructive pulmonary emphysema This strongly suggested that some of the bullae or cysts had poor or no communication with the air passages at the time of study. The ratio of residual volume to total lung capacity (RV/TC) was unusually high The ratio of FRC/TC $\times$ 100 was unusually high in all but the patient having the least degree of associated emphysema. Studies in the supine position showed the arterial CO_2 content to be high in 3 and normal in



FIG 16—(A) Demonstrates large bulla on plain film without indicating vascularity of adjacent compressed lung (*B and C*) Pulmonary arterial and venous phases of angiography showing compressed finer vasculature of potentially useful lung tissue.



Fig 17 —P A roentgenogram before and during pulmonary angiography Patient had bullae with poor bronchial communications and pulmonary emphysema Pattern contrast media in right ventricle suggests hypertrophic changes



Fig 18 —Pulmonary angiograms taken (A, *left*) before excision of large bulla of right upper lobe with concomitant pulmonary plexectomy (B, *right*) After surgery Note increase in finer vasculature right lung as well as improved position of vascular trunks

3; arterial oxygen saturation was decreased in 4 of the 6 patients There seemed to be a reasonable correlation between the ratio of residual volume to total lung capacity and the arterial oxygen saturation. The breathing reserve in this patient group was considerably decreased being 29 L. compared to 63 for the normal. The authors noted the similarity of these changes to those seen in patients with obstructive pulmonary emphysema except for the decrease in total lung capacity and the smaller than expected increase in residual volume. Measurement of the gas content of a large bulla in one patient indicated that the tension of oxygen and carbon dioxide aspirated from the air cyst was similar to that of mixed venous blood, sug-

gesting minimal bronchial communication The cyst showed no significant change in size on fluoroscopy or on biphasic roentgenographic study It was suggested that good bronchial communication would result in a considerable increase of residual volume Kaltreider and Fray were particularly interested in the dyspnea associated with these lesions, which they explained as follows:

> . . dyspnea in individuals with congenital cystic disease of the lung and emphysematous bullae may be readily explained by mechanical impairment of the respiratory bellows This impairment causes increased respiratory effort in the presence of decreased ventilatory reserve

The important contribution of Baldwin and her co-workers to our understanding of the pathophysiology of these lesions was based on a detailed study of 16 patients The patients were divided into the three groups according to (a) the nature of the bronchial communication with the lesion and (b) the functioning state of the remaining lung.

Group I. In this group there were 3 patients with free communication between the cyst and normal lungs. The physiologic observations here revealed that: (1) The total lung volumes were relatively normal, and there was a minimal increase in the RV/TC ratio in all three patients; (2) the maximum breathing capacity was normal, and the spirogram revealed a normal pattern, (3) in one of the 3 patients there was hyperventilation at rest, but hyperventilation was noted in all patients during standard exercise and the first minute recovery following exercise. The breathing reserve was large in all 3 patients, and only one presented slight dyspnea during the first minute recovery from exercise, (4) the rate of oxygen removal was significantly decreased at rest and exercise, but the total oxygen consumption during standard exercise was not reduced, (5) the index of intrapulmonary mixing was normal in all 3 patients, (6) the oxygen saturation at rest and with exercise was normal; (7) bronchospirometric examination was done in one patient revealing a considerable dead space ventilation in that instance suggesting a wide ve...

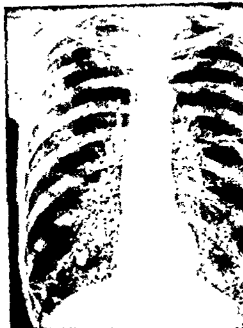


Fig 19 —P A roentgenogram taken 8 y... lipiodol bronchography illustrating effect of ... emphysema upon lymphatic channels I... residual lipiodol suggests destruction of ly...

tilation of areas poorly or not adequa... fused with blood, presenting primarily... space problem, and although the rat... exchange was inefficient, arterial ox... saturation was not presented The al... in regard to the size and distribution of... volume components plus a relatively... maximum breathing capacity sugges... the bronchial communications with... cysts were probably free Since the b... reserve was reduced in all states of ac... abnormal hyperventilation, the thre... dyspnea was reached during relativ... exertion.

Group II The second group con... three patients with large air cysts but p... munications with the air passages, alth... sociated with normal lungs. A summa... physiologic observations shows: (1) ... lung capacity here was moderately to... restricted, (2) maximum breathing ... was severely reduced in two and mode... in one; (3) the spirogram showed ev... expiratory obstruction and air trappi... regularity and asynergy of respirato...

(4) moderate hyperventilation was noted during the last minute of exercise. At rest and during the recovery period there was only minimal increase in ventilation. The breathing reserve during a minute of exercise, and the first minute of recovery, was noted to be greatly reduced, (5) the index of intrapulmonary mixing was high in one and normal in the other two, (6) the total oxygen consumption and rate of oxygen removal was relatively normal; (7) the arterial oxygen saturation and the P_{CO_2} were normal, (8) on 2 patients bronchospirometry was performed and showed a significant decrease in vital capacity and oxygen uptake of the side of the defect The ventilation of this lung was depressed but to a lesser extent. The chief disability in this group, therefore, was ventilatory insufficiency due to mechanical interference with the bellows action of the chest

Group III (IIIa) This subgroup consisted of patients with air cysts which communicated poorly with the air passages These patients also had chronic obstructive hypertrophic emphysema The disability here was noted to be due to ventilatory insufficiency A summary of the physiologic considerations showed (1) The total lung capacity was low despite an increase in the residual volume, the ratio of residual volume to total lung capacity was, therefore, increased, (2) the maximum breathing capacity was severely restricted but was able to improve with bronchodilators, (3) the spirogram revealed expiratory slowing and air trapping (Fig 20), (4) hyperventilation was noted during exercise and the period of recovery, the breathing reserve was greatly reduced, (5) the index of pulmonary mixing was high in 3 of the 4 patients studied, (6) the total oxygen consumption, the rate of oxygen removal, and arterial gas content were found to be relatively normal; (7) in one case bronchospirometry was performed revealing that the affected lung contributed its share to the total vital capacity and total ventilation and total oxygen consumption. In summary, the major disability in this group is severe ventilatory insufficiency There is a marked increase in the residual air to total lung capacity ratio indicating extensive chronic pulmonary emphysema The high index of intrapulmonary mixing indicates marked disturbance of the distribution of inspired air. *According to Baldwin: "... with the possible* exception of a reduced total capacity, the functional pattern of these cases is indistinguishable from that described for cases of chronic pulmonary emphysema with predominantly ventilatory insufficiency"

Group IIIb In the next subgroup of the third category were patients with cysts with poor communications associated with diffuse emphysema In these cases, the patient's disability was due both to ventilatory and alveolar respiratory insufficiency The physiologic observations here showed (1) some restriction of the total lung capacity despite a high residual volume in 5 of the 6 patients investigated; the residual volume to total lung capacity ratio was high, (2) the maximum breathing capacity was less that 20 per cent in 3 of 5 patients, (3) spirographic evidence of expiratory obstruction and air trapping was seen; (4) hyperventilation was seen in 2 patients who had the highest values for maximum breathing capacity while hypoventilation was noted in the others who had a greatly limited ventilatory capacity, (5) the index of intrapulmonary mixing was abnormally high in 3 of the 6 patients, (6) the oxygen consumption was reduced during exercise in cases unable to hyperventilate, (7) all cases revealed arterial hypoxia following exercise The arterial saturation was normal in only two at rest, and these showed lesser degrees of restriction of maximum breathing capacity The P_{CO_2} was normal in 3 of 4 patients in which this was tested In summary, the major difficulty in this group is revealed to be a combination of ventilatory insufficiency and marked alveolar respiratory insufficiency. Baldwin summarized: "The respective part played in the development of arterial anoxia by unequal ventilation-perfusion relationship and impaired diffusion of respiratory gases cannot be precisely defined"

In summary then, the functional disability of cases with large air-containing lesions of the lung appears to vary according to the nature of their bronchial communication and the state of the remaining lung Pulmonary function studies in unilateral cases may help define the

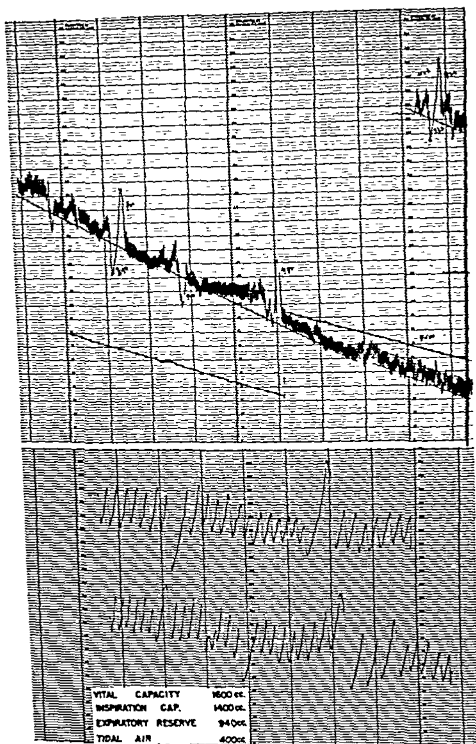


Fig 20 —Slow and fast speed bronchospirometric tracings seen in two patients with bullae having poor bronchial communications Note the small amplitude of deep and tidal air breaths. The progressive return of the respiratory tracing to a lower level after forceful expiration of vital capacity determination suggests bronchial obstruction and/or air trapping

TABLE 2 —*Studies Before and After Surgical Excisional Therapy for Bullae With and Without Good Bronchial Communication**

Study Performed	Case 3 female, 23 yr, 165 cm tall, wt 49 5 Kg, B S area = 1 53 Small diffusely cystic rt lung Cysts freely communicating with bronchi Rx total pneumonectomy			Case 5 male, 27 yr, 178 cm tall, wt 62 1 Kg, B S area = 1 78 Giant emphysematous bulla rt upper lobe Cyst communicating poorly with bronchi Rx lobectomy		
	Before Op	After Op	Predicted	Before Op	After Op	Predicted
Lung Vol in cc. (% predicted normal in paren)						
Vital capacity	2,450 (77%)	2,251	3,190	2,890 (66%)	3,865	4,375
Residual Air	1,189 (149%)	930	800	780 (71%)	1,890	1,095
Total capacity	3,679 (92%)	3,181	3,990	3,670 (67%)	5,755	5,470
$\frac{\text{Residual Air}}{\text{Total capacity}} \times 100$	32	29	20	21	33	20
Max Breath Cap (L /min)	73 (78%)	80	93	77 (60%)	117	128
Vent and Br Reserve						
Vent L /min /M²/B S						
Basal	6 6	3 5	3 3	4 1	6 2	3 6
1 min st exercise	14 6	10 6	10 2	15 7	12 4	11 0
1 min recovery	17 3	20 8	11 8	15 5	12 8	12 5
Br Reserve/MBC × 100						
1 min st exercise	52	65	68	49	95	109
1 min recovery	47	61	76	49	94	106
Index Intrapulmonary mixing alveolar N_2%/7 min pure O_2	1 05	1 20	<2 5	5 5	4 6	<2 5
Oxygen consumption cc/min /M²/B S						
Basal	128	—	—	162	—	—
1 min st exercise	461	—	—	710	—	—
O_2 intake cc/L vent						
Basal	22 6	44 0	45 0	44 4	31 1	47 1
1 min st exercise	36 4	45 8	56 5	51 5	54 6	56 2
Respiratory gasses (rest and exercise)						
Arterial oxygen sat %						
Basal	98	96	96	96	96	96
1 min recovery	96	97	96	94	93	96
Car dioxide cont (Vol %)						
Basal	43 8	—	—	44 4	—	—
1 min recovery	42 9	—	—	39 2	—	—
Car dioxide tension (mm Hg)						
Basal	—	—	—	36	37	44
1 min recovery	—	—	—	33	43	43
Car dioxide content at 40 mm Hg						
Basal	—	—	—	46 5	—	—
1 min recovery	—	—	—	43 0	—	—
Bronchospirometry (R lung)						
% total vital cap	43	—	55	16	46	55
% total ventilation	66	—	55	31	59	55
% total O_2 intake	0	—	55	13	46	55

* Data represent a composite of data from Table 1–7 of paper of Baldwin, et al [6]

indications for and actually tend to predict the results of surgery. The primary dysfunction in cases with free communication with the air passages is hypoventilation due to poorly diffused areas resulting in an inefficient rate of gas exchange and compensatory hyperpnea.

Effects of Surgical Excision of Bullae or Cysts on Pulmonary Physiology

Preoperative and postoperative pulmonary function studies have been presented by several authors. Baldwin[6] recorded the results in two types of patients. In the first patient belonging to Group I of large cysts with free communication (with air passages) and apparently normal lungs, a copy of the findings is shown in Table 2 and may be summarized as follows. Prior to operation, the basic changes noted were: (1) marked hyperventilation, (2) low rate of oxygen removal both at rest and during exercise, (3) minimal restriction of total lung volume and maximum breathing capacity, (4) bronchospirometry of the right lung revealed that it was carrying out 66 per cent of the total ventilation without any respiratory gas exchange. Following surgical resection of a large bulla on the right, the re-evaluation studies demonstrated: (1) a decrease of 550 cc. in total lung volume evenly distributed between the vital capacity and the residual air, (2) ten per cent improvement in maximum breathing capacity and (3) return of the rate of oxygen removal to normal.

In the second group of patients belonging to Group II, there were preoperative and postoperative studies on 2 patients. These were patients with large air cysts with poor communications with the air passages and in association with apparently normal lungs. In both these patients the preoperative studies revealed: (1) significant restriction of the total lung volume, vital capacity and maximum breathing capacity, (2) hyperventilation with decreased breathing reserve during standard exercise tests, (3) a high index of intrapulmonary mixing associated with normal respiratory gas exchange and normal gas contents in the arterial blood, (4) a negligible oxygen intake of the involved lung was revealed on bronchospirometry. Following surgery th[illegible]

(1) a significant increase in total lung capacity and vital capacity; (2) return of the breathing reserve and ventilation to normal; (3) the bronchospirometric studies revealed a normal ventilation and oxygen intake of the operated lung, and (4) in one of these patients an increase in residual volume following surgery was noted. The explanation of this is not clear.

Physiologic studies relative to the effect of surgery in Baldwin's Group IIIa, (air cysts with poor communication plus chronic emphysema) suggested that disability was due to ventilatory insufficiency. Preoperative studies showed: (1) restricted total lung capacity with increased residual volume, (2) severe restriction of maximum breathing capacity, (3) a slight hyperventilation at all times with some decrease of breathing reserve on standard exercise tests. Postoperative examination demonstrated: (1) marked increase in total lung capacity, 75 per cent of which involved an increase in vital capacity, therefore, the residual volume to the total lung capacity ratio was decreased from 47 to 37 per cent; (2) a marked increase in maximum breathing capacity; (3) a significant increase in breathing reserve, and (4) an unexplained postoperative increase in residual volume.

Single case reports involving physiologic studies done before and after surgery have also been presented by Warring and Landskog,[40] and by Boren.[8] Warring and Landskog's patient showed a significant reduction in vital capacity prior to surgery with a return almost to normal after bilateral resection of giant cysts. Maximum breathing capacity increased remarkably and progressively over a period of 29 months after the operative procedure. There was prompt improvement of ventilation in 2 weeks. Some degree of arterial oxygen desaturation was noted both before and after surgery in the basal state, but not with exercise. The dyspnea at rest and on severe exercise was eliminated by the operative procedure.

The studies by Boren ascribed to surgery: (1) a significant increase in vital capacity, (2) marked improvement in the maximal speed of expiration, (3) significant increase in the value for maximal midexpiratory flow and (4) total

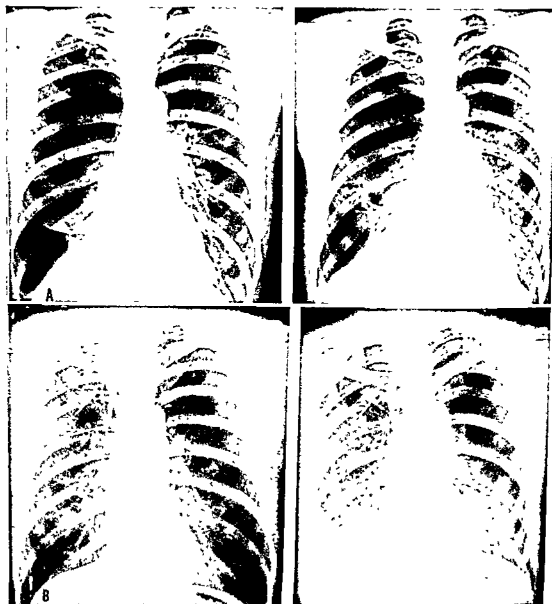


FIG 21 —(A) Preoperative inspiration-expiration roentgenographic study of H C W suffering from multiple large bullae and advanced diffuse obstructive pulmonary emphysema (B) Inspiration-expiration study following excision and plication of multiple bullae plus pulmonary plexectomy

FIG 21 —(C) Preoperative and postoperative ventilatory function study (bullous emphysema)

Patient H C W	Preoperative	Postoperative (14 mos)
Maximum breathing capacity	51 4 L /min	88 0 L /min
Walking ventilation	26 8 L /min	25 0 L /min
Dyspnea index	0 52	0 28
Per cent reserve, MBC-W V /MBC	48%	71 6%

desaturation at rest Bronchospirometric examination showed definite improvement in the oxygen consumption, minute ventilation and vital capacity of the surgically treated lung

We have been able to study some patients who had large emphysematous bullae in association with pulmonary emphysema In these patients, the bulla was surgically resected and varying types of pulmonary denervation were performed The results of these studies are presented in FIGURE 21.

Studies of Vascular Dynamics of Bullae and Cysts

We have studied by cardiac catheterization a limited number of patients with emphysematous bullae and pulmonary emphysema.[4] The findings are frequently those seen in obstructive hypertrophic pulmonary emphysema. The cardiac output tends to be normal or high depending in general on whether anoxia is present. The cardiac output may increase normally in response to exercise or may fail to increase. Normal or reduced values for circulation time are usually noted. Venous pressure may be within normal limits or elevated. In some instances, right ventricular and pulmonary artery pressures were increased and showed a significant rise during effort. In one patient with bullous emphysema with a valvelike obstruction and apparently normal lungs, cardiac catheterization revealed a definite elevation of pulmonary artery pressure in response to exercise, which could not be changed by the administration of large doses of atropine intravenously.

Another patient with bullous emphysema but with poor bronchial communications and associated diffuse obstructive pulmonary emphysema also had an elevated pulmonary artery pressure at rest which increased significantly on exercise. This response could not be changed by atropine. In another patient, in which the bullous component of the disease had a good bronchial communication and the remaining lung structure showed significant emphysema, the rise in pulmonary artery pressure attendant to exercise could be eradicated by the administration of atropine.

We have been able to study patients of this type at the time of thoracotomy. Procaine block of either the sympathetic or vagus nerves to the lung produces no essential change in pulmonary arterial or venous dynamics in patients having bullae with or without any type of air communication, if the remaining lung tissue is free of disease. If there is a significant emphysema in conjunction with the disease, the changes are those expected with pulmonary emphysema. When there is free communication of bullae with the air passages, the administration of high ventilation pressures through an endotracheal tube in the presence of an intact chest wall has been noted to produce a paradoxical pulse and to decrease the systemic arterial blood pressure.

Direct measurements of pulmonary venous pressure at the time of thoracotomy on patients with combined bullous and hypertrophic emphysema have been made by us on a few patients.[4] Present evidence would suggest that a normal or elevated pulmonary venous pressure seen in this group tends to decrease in response to procaine block of the vagus nerve. If the ventilation pressure is appreciably increased in the presence of air cysts with valvelike communication allowing progressive distension, the pulmonary venous pressure tends to fall. If the distension progresses, there will be a resultant fall in systemic arterial pressure and cardiac output. When a patient with bullous emphysema has associated bronchospastic states, procaine block of the pulmonary vagus nerve components may (1) decrease the pressure in the pulmonary artery and the pulmonary vein or (2) significantly increase the reflection of the air ventilation pressure on the pulmonary arterial or pulmonary venous pressure curves.



Fig 22.—Pulmonary angiogram performed by Dr B L Brofman utilizing unilateral pulmonary artery occlusion. Note the marked downward displacement of all branches of the right pulmonary artery secondary to severe bullous emphysema. (Reprinted by permission from Intravascular Catheterization, edited by H A Zimmerman, Charles C Thomas, publisher.)

We are now in the process of repeating this type of study in the operating room with constant pressure, variable volume ventilators. If there is free bronchial communication with the bulla, clamp occlusion of the bulla significantly decreases the volume of air delivered to the patient's lung at a standard ventilation pressure Studies of this type as well as direct visual inspection afford another means of defining the type of air communication present in these lesions

Brofman[10] has recorded the response of unilateral pulmonary artery occlusion performed with a double lumen catheter (Fig. 22). H[e] states.

> In a patient with severe bullous emphysema, con[-]trol pressures in the pulmonary artery and righ[t] ventricle were significantly elevated Following occlu[-]*sion of the left pulmonary artery, there was* littl[e] change in right ventricular pressure while the dista[l] (lacunar) pressure in the right pulmonary artery fell Arterial saturation was unchanged .. The hig[h] *ventricular, pulmonary artery, and lacunar pressure*[s] are influenced by the marked intrapleural pressur[e] variations

This author has demonstrated the downwar[d] displacement of a pulmonary artery adjacent

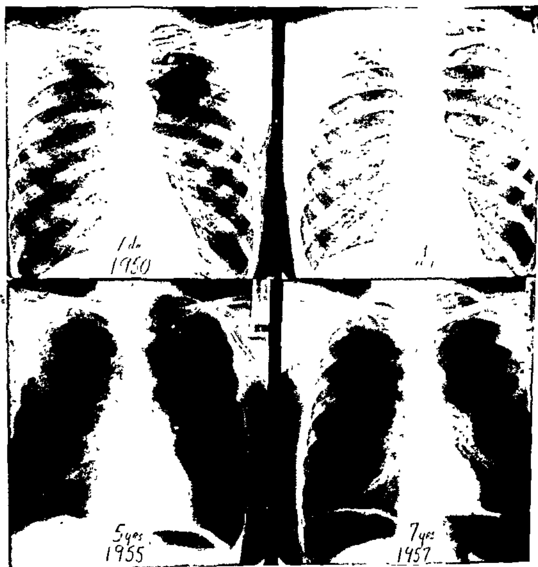


Fig 23 —Serial roentgenographic study over a period of seven years showing that nonsurgically treated bullous emphysema can progressively destroy lung tissue Patient was never offered surgery and died with cor pulmonale in 1957

to a large bulla by injecting contrast media distal to the occlusion of the artery.

Therapeutic considerations. Where there is a persistent pneumothorax due to a bulla or bleb, the need for direct surgical excision is obvious. However, a relatively small cyst or bulla which neither communicates with the pleural space or the bronchial tree nor disturbs the function of adjacent lung parenchyma may be treated either by periodic observation or more radically by prophylactic excisional therapy. Larger lesions may gradually destroy contiguous lung tissue or may vary in their type of bronchial communication (Fig. 23). In such lesions, excisional therapy serves both to prevent further damage and to improve pulmonary function. If irreversible changes in adjacent lung tissue are found, early surgical resection is indicated. The major problem of surgery is the determination of the type of respiratory insufficiency produced by the associated emphysema. When large air cysts and diffuse emphysema are associated with arterial oxygen desaturation at rest, there may be too much irreversible disease of the lung to allow a satisfactory response to surgical excision. Whenever the functional pattern presented by patients with bullae having poor or intermittent communications and associated with emphysema demonstrates the insufficiency is predominantly ventilatory, surgery should be tried in patients of this type. The author has been investigating the possible value of pulmonary denervation in conjunction with excision of bullae in patients of this type, and long-term results suggest that this procedure may be of value (Fig. 24).

The technical considerations of the surgical procedures need be only briefly mentioned. Persistent pneumothorax due to a small bleb or bulla requires simple excision of the defect plus decortication if lung expansion is restricted. Large cysts without bronchial com-

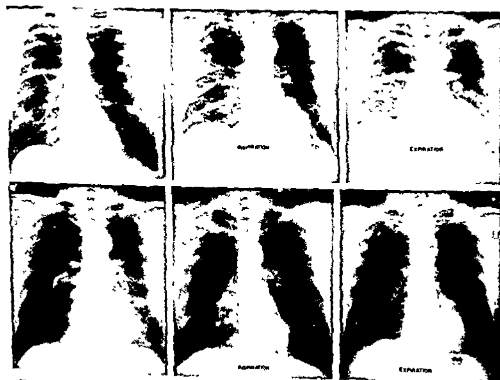


Fig. 24.—S... trophic ...

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munication may be locally excised in the intact state Infected congenital cysts require segmental resection or occasionally lobectomy. Extensive replacement of lung tissue by congenital cystic disease may necessitate lobectomy.

The surgical management of large bullae may be divided into three categories If the patient's general condition precludes primary surgical excision, the external drainage procedures should be employed incorporating Monaldi-type intracavitary suction suggested by Head and Avery [20] The direct surgical corrective procedures have been well described by Claggett,[12] Rumel,[34] Dugan and Samson,[16] Naclerio and Langer,[30] Cooke and Blades[13] and others. One must be aware of the acute respiratory and circulatory disturbances which may be attendant to progressive overdistention of a bulla on induction of anesthesia There appears to be distinct merit in the use of negative pressure ventilation during expiration throughout the anesthesia. Initially, the surgery of bullae utilized simple plication maneuvers, but disturbing postoperative lung air leaks and frequent recurrence forced discontinuance of this method. It is desirable to open the bulla widely, identify and correct all air communications with the bronchi, excise the redundant tissue and then reconstruct the pleural surface We have found great value in multiple-layer closure of the raw lung surface with very fine (no 5-0) silk on straight atraumatic needles Drainage with multiple thoracotomy tubes and frequent bronchoscopy may be needed to prevent persistent air leaks or extensive subcutaneous emphysema

When extensive pulmonary emphysema is found together with bullae, surgery is unwise if the combined defects produce arterial anoxia and the disability is both ventilatory and alveolar respiratory insufficiency. We are investigating the value of a surgical procedure in this group incorporating (a) excision of major bullae and areas of excessively distended emphysematous lung tissue, (b) total pulmonary denervation and (c) initiation of temporary pneumoperitoneum through the exposed hemidiaphragm.

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Section IX

CHEST DISEASES WITH BOTH OBSTRUCTIVE AND RESTRICTIVE COMPONENTS

Interstitial Diseases of the Lung: The Alveolar-Capillary Block Syndrome

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SINCE the 1920s it had been postulated that certain types of diffuse pulmonary fibrosis produced pulmonary insufficiency by interfering with the diffusion of respiratory gases between alveolar air and capillary blood. Austrian and his colleagues[1] were the first to measure pulmonary diffusing capacity in a group of pathologic conditions always associated histologically with involvement of the alveolar-capillary membrane. They found markedly decreased values for the diffusing capacity of the lung for oxygen, and coined the name "alveolar-capillary block" syndrome. Although the causes were numerous, the syndrome had distinct clinical, physiologic and pathologic features, which were the result of diffuse interstitial pulmonary disease. Their concept has been amply verified and extended by later investigators.

Etiology and Natural History

Since the cause of many of the numerous diseases which may produce significant disturbances in alveolar-capillary diffusion is unknown, any etiologic classification proves quite unsatisfactory at present. The natural history of many forms of diffuse lung disease is sufficiently varied to contribute to a useful clinical classification. The rapidity of onset and the progress of the disease provide the basis in the following classification for the primary categories under which the various diseases are classified into broad etiologic subgroups:

Acute or Subacute

Infectious agents[9]
1. influenza[40]
2. other virus pneumonias[11]
3. varicella[18]
4. miliary tuberculosis[22]
5. miliary fungus infection[4]
6. possibly, the acute diffuse interstitial fibrosis described by Hamman and Rich[20]

Noxious agents
1. irritating gases such as chlorine, phosgene, sulphur dioxide[2] and oxides of nitrogen (Silo-Filler's disease)[17-21]
2. beryllium[14-21]
3. organic irritants such as moldy forage (Farmer's lung), which are only mild primary irritants and probably produce a delayed allergic reaction[10, 14]

Tissue changes associated with generalized systemic disease
1. uremia[23-29]
2. acute disseminated lupus erythematosus[31, 48]
3. acute polyarteritis nodosa[43]
4. acute disorders associated with pulmonary eosinophilia[7-13]

Insidious

Noxious agents (pneumoconioses)[27]
1. beryllium[16-21]
2. asbestos[44-49]
3. diatomaceous earths[46]
4. talc[19]
5. occasionally silica[12-27]

Generalized disease of unknown etiology
1. sarcoidosis[30-33]
2. polyarteritis[43]
3. disseminated lupus erythematosus[36, 48]
4. scleroderma[26]
5. *necrotizing granulomatosis*[25]
6. pulmonary histiocytosis[29, 42]
7. lymphogenous carcinomatosis including lymphomas and pulmonary adenomatosis[15, 38]
8. pulmonary alveolar microlithiasis[3]
9. primary pulmonary hemosiderosis[24]
10. chronic diffuse interstitial fibrosis of unknown etiology (frequently termed Hamman-Rich syndrome)[1-20]

Many of these diseases are slowly progressive, a few show a natural tendency to improve, while others exhibit a fluctuating course. In some, the course of the disease is influenced by appropriate therapy, while others follow a relentless downhill course in spite of all treat-

ment The information which the writers have found useful in suggesting the correct etiology is summarized in TABLE 1. In addition, it should be noted that cardiac failure and the pulmonary vascular abnormalities observed in such diseases as mitral stenosis or primary pulmonary hypertension may produce a very similar syndrome.[6, 34] For a more detailed account of these and other causes of disturbances in pulmonary diffusion the reader should refer to Chapter 39

As in all clinical medicine, a careful and complete history is essential. Direct and detailed questions regarding every job held by the patient may be necessary in order to uncover a history of exposure to a potentially noxious agent Too often, the interrogator fails to inquire about the patient's occupations prior to his present one Even "unemployed" is accepted as an occupation in some medical records The history should include the type of work performed, the dates of each period of employment and the nature of all materials handled A delayed response or hypersensitivity to previously tolerated materials may obscure the causal relationship between exposure and onset of symptoms

SYMPTOMS

The outstanding symptom is exertional dyspnea Unless the disease is acute or far advanced, the patient is usually comfortable at rest. Easy fatigability, lassitude, general malaise, anorexia and weight loss are not uncommon Except, however, for diseases due to infectious agents or showing allergic features, fever is slight or absent A history of chills and fever is, therefore, of considerable diagnostic importance Where infection or hypersensitivity can be excluded, a low-grade fever suggests the presence of a collagen disease or neoplasm. Cough is common and severe paroxysms may be produced by exertion or forced deep breathing Unless there is an associated bronchitis, the sputum is neither copious nor purulent. A history of chills, fever, cough and dyspnea following within a few hours of exposure to moldy organic forage is almost pathognomonic of the Farmer's lung syndrome,[10, 14] but in most other instances the symptoms are not specific enough to establish the diagnosis

PHYSICAL EXAMINATION

Physical examination of the chest may reveal surprisingly few abnormalities until the disease is far advanced. A few fine basal rales and high-pitched expiratory squeaks on forced expiration may be the only physical manifestations of the acute or early stages of disease. The extent of roentgenographic abnormality may come as quite a surprise to the clinician in face of such paucity of physical findings. Tachypnea is present at rest and after exercise. Although some degree of arterial oxygen unsaturation may exist at rest, it is rarely severe enough to be clinically recognizable, although, with exertion, marked cyanosis may become apparent. Clubbing of the fingers is inconstant and polycythemia rare With advanced disease, there is limitation of thoracic movement and alteration of the breath sounds, but bronchial breathing or other signs of consolidation are rare. In the terminal phase, accentuation of the second pulmonic heart sound heralds the onset of pulmonary arterial hypertension, and chronic right heart failure eventually supervenes When a patient is seen for the first time at this stage, the pulmonary cause of the disease may be obscured by the cardiovascular abnormalities present It is obvious, therefore, that physical examination of the chest provides little if any diagnostic information In general, however, the presence of widespread fine crepitant rales throughout both lungs points to the more acute and inflammatory forms of disease, while their absence is more characteristic of the chronic fibrotic or neoplastic processes A few of the diseases listed in TABLE 1, such as sarcoidosis and diseases of collagen tissue, may produce diagnostic changes in other organs. To mention only two, the uveoparotitis of sarcoidosis and the skin changes of scleroderma are quite characteristic.

ROENTGENOGRAPHIC EXAMINATION

Chest roentgenograms[38] are essential to the evaluation of any patient with suspected pulmonary disease. However, in this group of

TABLE 1.—*Diagnostic Features in Various Forms of Pulmonary Disease (Arranged in Order of the Rapidity of the Clinical Course)*

Disease	Onset	Causative Agent	Course	Generalized Disease	Diagnostic Aids	Roentgenogram	Biopsy	Treatment
1. Influenza	Acute	Influenza virus	Acute	+	Isolation of virus serologic tests	Rapid development and clearing	Not indicated	
2. Virus pneumonia	Acute	Probable virus	Acute	±	Rising titer of cold agglt, M G strept agglt	Rapid development and clearing	Not indicated	? Response to tetracyclines
3. Varicella	Acute	Varicella virus	Acute	+	Characteristic skin lesion	Rapid development and clearing	Not indicated	
4. Acute granulomatous infections	Acute to subcute	Tubercle bacillus, H capsulatum, B dermatitidis, C immitis	Acute Subacute	+	Skin tests, C F tests, recovery of causative agent by culture	Usually distinct miliary densities, pleural effusions may occur	Smear and culture of resected tissue essential, acid fast and special fungus stains	Isoniazid, P A S and streptomycin, amphotercin B, corticosteroids ?
5. Hamman—Rich syndrome	Acute to subacute	Unknown (? virus)	Acute and progressive	–	Only lung biopsy diagnostic	Diffuse progressive interstitial fibrosis	Lung biopsy quite characteristic Hyaline membrane and proliferation of alveolar cells	Corticosteroids
6. Pneumonitis due to noxious fumes	Acute	Noxious gases such as chlorine, sulfur dioxide and nitrogen dioxide	Acute with slow recovery, permanent damage common	–	Occupational history	Acute pulmonary edema, chronic residual interstitial fibrosis and emphysema	Obliterative bronchiolitis	Corticosteroids
7. Acute beryllium pneumonitis	Acute	Beryllium	Acute with recovery—may progress to chronic	±	Occupational history, beryllium patch test	Acute pneumonitis	Acute pulmonary edema, not granulomatous in acute phase	Corticosteroids
8. Farmers lung	Acute to chronic	Probable sensitivity to molds or products of molds	Acute, recurrence common with reexposure	–	Exposure to moldy forage, acute chills, fever & dyspnea, rarely necessary to do lung biopsy for diagnosis	Acute interstitial pneumonia—clears rapidly, chronic disease—patchy fibrosis; interstitial fibrosis	Acute granulomatous interstitial pneumonia	Corticosteroids
9. Uremia	Acute	Beta hemolytic Streptococcus	Acute	+	Characteristic urine sediment	Acute pulmonary edema which clears rapidly	Not indicated	Corticosteroids

10 Pulmonary eosinophilic changes	Acute	Hypersensitivity to numerous drugs and other allergens	Acute, recurrences common	?	Eosinophilia common, eosinophiles in sputum	Acute patchy pneumonitis shifting rapidly	Rarely necessary in eosinophilic pneumonitis	Corticosteroids
11 Polyarteritis	Acute to subacute	Unknown	Acute to subacute, recurrent	+	Eosinophilia, anemia and other evidence of multiple system disease	Acute interstitial changes which clear rapidly but tend to recur	Muscle and kidney biopsy frequently shows the polyarteritis	Corticosteroids
12 Disseminated lupus erythematosus	Acute to subacute	Unknown	Acute to chronic, recurrent	+	L E cells in peripheral blood or bone marrow, fluorescent antibodies	Acute interstitial changes which clear rapidly but tend to recur; pleural changes frequent	Lung biopsy not as diagnostic as the L E cells; kidney biopsy helpful	Corticosteroids
13 Chronic beryllium poisoning	Insidious	Beryllium	Progressive	+	Occupational history, beryllium patch test	Interstitial patchy pneumonitis, peripheral emphysema marked in late stages	Lung granulomatous lesion; beryllium in tissue	Corticosteroids
14. Asbestosis	Insidious	Asbestos	Progressive	−	Occupational history	Shaggy pleural and pericardial adhesions with interstitial fibrosis	Lung—only diagnostic if asbestos body found in fibrotic tissue of lung or pleura	None
15 Silicosis	Insidious	Silica	Progressive	−	Occupational history	Usually nodular with some conglomerate density—rarely a finely diffuse interstitial fibrosis	Lung—"whorls" in the intensely fibrotic nodules	None
16 Pneumoconiosis due to diatomaceous earths	Gradual	Calcinated diatomate most hazardous	Progressive	−	Occupational history	Diffuse interstitial change, pneumonitis not uncommon	Lung—not unlike changes of silica	None
17. Sarcoidosis	Insidious	Unknown	Varies widely	+	Kveim test, hypercalcemia, hypercalciuria; increased serum globulin, characteristic uveal tract and skin lesions	Lung-"potato" hilar adenopathy early, later diffuse miliary and patchy parenchymal change with less evident adenopathy	Scalene node—frequently shows the characteristic noncaseating granuloma	Corticosteroids

TABLE 1.—*Diagnostic Features in Various Forms of Pulmonary Disease (continued)*

18. Scleroderma	Gradual	Unknown	Progressive	+	Skin changes quite characteristic	Diffuse interstitial changes more marked in lung bases, pleural changes not infrequent	Skin biopsy characteristic	Corticosteroids ? Chelating agents
19. Necrotizing granuloma	Gradual	Unknown	Progressive	+	Lesions of nose and paranasal sinuses, kidney involvement common	Nonspecific diffuse changes	Necrotizing granulomatous angiitis skin and kidney as well as pulmonary lesions	Corticosteroids
20. Lymphogenous carcinomatosis, lymphomata, adenomatosis	Gradual	Unknown	Progressive	±	Sputum smears may show malignant cells	Hilar adenopathy frequent, pleural changes common, destructive bony lesion diagnostic	Characteristic cells in scalene nodes Lung biopsy may be necessary in pulmonary adenomatosis	Roentgen therapy, corticosteroids, cancer chemotherapy
21. Pulmonary histiocytosis	Insidious	Unknown	Progressive but wide variety	+	Bone involvement characteristic	Interstitial changes, "honeycomb" lung late	Lung-diffuse histiocytic infiltration early, later intensive fibrosis with a few nests of lipophages	Roentgen therapy, Corticosteroids
22. Microlithiasis alveolaris pulmonale	Insidious	Unknown	Progressive but slow	−	Dependent on x-ray	Characteristic microlithiasis	Lung biopsy rarely necessary	None
23. Primary pulmonary hemosiderosis	Insidious	Unknown	Progressive	−	Hemosiderin in macrophages in sputum	Transient miliary densities early then gradually increasing and persistent interstitial changes	Fibrosis of lung with hemosiderin deposits	? Corticosteroids
24. Chronic diffuse interstitial fibrosis	Gradual	Unknown	Progressive	−	Only lung biopsy diagnostic	Chronic interstitial changes	Fibrosis of lung, scalene node biopsies usually not helpful	? Corticosteroids

diseases they are rarely diagnostic. There is usually an increase in the truncal markings accompanied by a somewhat veiled hazy appearance and diffuse granular or mottled densities. Distinct miliary or nodular lesions are present in some instances Fibrotic lesions can usually be distinguished from the more acute inflammatory lesions by their sharp dense character. When more than the interstitial structures of the lung are involved, coarse nodular or linear densities are usually present. It should be emphasized, however, that a fairly marked degree of interstitial change may be present without any recognizable roentgenographic abnormality Hilar or paratracheal adenopathy of significant degree is rare except in patients with Boeck's sarcoid Pleural changes are unusual save for patients with asbestosis, fungus infections, tuberculosis or one of the collagen diseases Spontaneous pneumothorax may occur occasionally secondary to rupture of emphysematous blebs, which are commonly seen in the advanced stages of interstitial fibrosis In general, however, chest roentgenograms *rarely* establish an etiologic diagnosis. The "potato" type hilar adenopathy of sarcoidosis and the peculiar calcification of alveolar microlithiasis are the only features which will allow the radiologist to arrive at an etiologic diagnosis Less frequently the presence of marked pleural thickening and obliteration of the costophrenic angles, together with a shaggy outline to the cardiac shadow and a fine groundglass appearance in the lower portion of the lung fields will permit a radiologic diagnosis of asbestosis The rate of development and clearing or progression of the interstitial changes once recognized is of considerable diagnostic value (TABLE 1). Finally, a careful inquiry should be made concerning the availability of previous chest roentgenograms for comparison

PULMONARY FUNCTION TESTS

For the past 30 years, clinicians and physiologists have postulated that thickening of the pulmonary membrane caused desaturation of arterial blood by interfering with the diffusion of respiratory gases Baldwin et al,[2] for example, demonstrated that, when other abnormalities in pulmonary function could be excluded, a defect in diffusion was the most reasonable explanation for the pulmonary insufficiency caused by certain types of diffuse pulmonary fibrosis. Austrian and his colleagues [1] were the first to measure diffusing capacity in a group of pathologic conditions always associated histologically with involvement of the alveolar capillary membrane. They found markedly decreased values for pulmonary diffusing capacity and coined the name "alveolar-capillary block" syndrome. Although the causes were numerous, the syndrome had distinct physiologic features, most of which are outlined in TABLE 2. These patients characteristically had a relatively normal maximum breathing capacity, hyperventilation at rest, reduced static lung volumes and an arterial saturation that was normal at rest but which fell markedly after exercise. As a result of hyperventilation, the

TABLE 2.—*Physiologic Features Usually Found in the Alveolar-Capillary Block Syndrome*

Test	Usual Result
Diffusing capacity	Decrease
A-a gradient at two levels of oxygenation	Increase
Arterial saturation at rest	Normal or slight decrease
Arterial saturation on exercise	Decrease
Arterial pH	Normal or increase
Ventilation at rest and on exercise	Increase
Alveolar oxygen tension	Increase
Ventilation equivalent	Decrease
Alveolar & arterial CO_2 tension	Decrease
Static lung volumes (VC, RV, TLC)	Decrease
Residual volume/total lung capacity	Normal
Maximum breathing capacity	Normal or slight decrease
Timed vital capacity	Normal
Lung compliance	Decrease
Tissue resistance	Increase
Airway or turbulent resistance	Normal
Work (elastic) of breathing	Increase
Index of intrapulmonary mixing	Normal
Single breath test (Fowler)	Increase
Dead space/tidal ventilation	Increase
Venous admixture in arterial blood	Increase
Air trapping on spirogram	Absent
Pulmonary arterial pressure	Increase
Pulmonary vascular resistance	Increase

TABLE 3 —*Diseases of the Lung in Which the Alveolar-Capillary Block Syndrome has been Demonstrated by Physiologic Tests*

Clinical Material Studied

Disease	References to Investigation
Acute sulfur dioxide poisoning	2, 5, 41
Alveolar cell carcinoma	41
Alveolar microlithiasis	3, 41
Asbestosis	2, 5, 26, 35, 41
Beryllium disease	1, 5, 6, 12, 34, 35, 41
Eosinophilic granulomas	35
Farmer's lung	10, 41
Granulomas of unknown etiology	1, 2, 5, 6, 12, 41, 47
Hamman-Rich syndrome	6, 41
Histiocytosis X	42
Infiltration with eosinophilia	13
Interstitial fibrosis of unknown etiology	1, 6, 31, 35, 37, 41, 47
Interstitial pneumonitis due to oil	41
Interstitial pneumonitis of unknown etiology	2, 12, 35, 41
Leukemia	18
Lymphangitic carcinomatosis	2
Miliary carcinomatosis	6
Miliary tuberculosis	5, 6, 12, 32, 35
Radiation fibrosis	45
Sarcoidosis	1, 5, 6, 32, 34, 37, 41
Scleroderma	1, 2, 5, 6, 12, 34, 35, 37, 41, 47
Silicosis	12, 26, 41
Silo-fillers disease	41
Talcosis	41

alveolar oxygen tension was high and arterial carbon dioxide tension low In severe cases, abnormalities of blood and gas distribution appeared (i e , there were increases in physiologic dead space and in venous admixture in arterial blood). Pulmonary arterial hypertension was frequently present These results have been amply verified by later investigators[26, 35] Thus, there has been added a physiologic concept, which has contributed significantly to our understanding of these diseases TABLE 3 lists the diseases of the lung in which alveolar-capillary block has been *demonstrated* by physiologic tests together with selected references.

The physiologic abnormalities encountered in diffuse interstitial pulmonary disease, in general, correlate well with the clinician's concept of the pathologic physiology as determined by clinical, roentgenographic and histologic examination.

TABLE 4 demonstrates three illustrative examples of the alveolar-capillary block syndrome. *In view of the extensive infiltration of* the lung with cellular or fibrotic tissue, reduction in static lung volumes with a relatively normal ratio of residual lung volume to total lung capacity is not unexpected. Since the alveolar-capillary membrane and interstitial tissue of the lung may be extensively involved in the absence of significant defect in the conducting airways, there is usually a reduction in lung compliance without much change in the resistance of the airways For the same reason, maximum expiratory flow rates, maximum breathing capacity and one second forced expiratory volumes ($FEV_{1.0}$) are relatively normal

The decrease in pulmonary diffusing capacity is most easily explained by an increase in the *thickness of the alveolar capillary membrane* However, utilizing the technique of Roughton and Forster, it can be shown[34] that there is also a considerable loss of pulmonary capillaries * Unlike primary vascular disease of the lung, the abnormality in the pulmonary membrane is proportionately greater than the loss of capillary bed (TABLE 4) Many teleologic and physiologic factors have been invoked to account for the marked hyperventilation which is associated with an increased alveolar oxygen tension and decreased alveolar carbon dioxide tension The most likely explanation is ab*normally powerful proprioceptive stimuli* from receptors in the pulmonary parenchyma, blood vessels or chest wall The persistently low arterial carbon dioxide tension and alkaline reserve which result may tend to perpetuate the

* Diffusion of gas in the lung can be considered as made up of two parts, that across the membrane and that inside the capillary. By an ingenious technic Roughton and Forster have shown that it is possible to measure the true diffusing capacity of the pulmonary membrane (D_M) and the volume of the pulmonary capillary bed (V_C) For normal subjects with a body surface area of about 2 M^2, D_M is approximately 60 ml /minute/mm. Hg and V_C 95 ml [34]

TABLE 4.—*Effect of Diffuse Interstitial Fibrosis on Pulmonary Function*

Test	Disease					
	Idiopathic		Scleroderma		Sarcoidosis	
	Pred	Obs	Pred.	Obs	Pred	Obs
LUNG VOLUMES						
Vital capacity (L.)	4.35	2.38	3.77	1.77	2.92	1.38
Residual volume (L.)	1.50	2.40	1.13	0.93	0.88	0.89
Total lung capacity (L.)	5.85	5.10	4.90	2.69	3.80	2.37
RV/TLC × 100 (%)	<40	47	<40	34	<40	37
MECHANICS OF BREATHING						
Maximum breathing capacity (L./min.)	110	155	90	140	84	95
1 second forced expiratory volume	83	100	83	98	83	100
Maximal expiratory flow rate (L./min.)	500	430	500	330	350	248
Maximal inspiratory flow rate (L./min.)	400	410	400	270	300	135
Lung compliance (L./cm H_2O)	0.20	0.06	0.20	0.05	0.20	0.04
Airway resistance (cm H_2O/L./sec.)	1.00	1.00	1.00	0.33	1.00	1.9
DISTRIBUTION OF INSPIRED GAS						
N_2 after 7 min. oxygen (%)	<2.5	<2.5	<2.5	<2.5	<2.5	<2.5
N_2 single breath (%)	<2.0	2.3	<2.0	6.3	<2.0	6.3
VENTILATION						
Resting respiratory rate (/min.)	12	26	12	26	12	40
Resting minute volume (L./min.)	6.0	18.1	6.0	13.0	6.0	18.7
DIFFUSION						
Arterial O_2 saturation (%)	96.0	—	96.0	91.9	96.0	96.8
A-a O_2 gradient breathing air (mm. Hg)	<10	—	<10	26	<10	45
Diffusing capacity of lung (ml./min./mm. Hg)	28.5	16.1	20.2	6.5	24.7	3.4
Diffusing capacity of membrane (ml./min./mm. Hg)	55	23.3	40	10.0	50	4.3
Pulmonary capillary volume (ml.)	85	62	60	28	75	25
Membrane resistance/intracapillary resistance	1.0	1.8	1.0	2.0	1.0	4.0

Physiological features in 3 patients with diffuse interstitial pulmonary fibrosis reported by McNeill, Rankin and Forster[34] arranged in order of severity of the disease together with the average normal values. By a special techn

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abnormal ventilatory drive by increasing the sensitivity of the respiratory center. In patients with stiff lungs, the minimal amount of work on the part of the respiratory muscles will be achieved at a rapid rate and small tidal volume. At rest, the increased alveolar oxygen tension tends to prevent any significant decrease in resting arterial saturation until diffusing capacity is less than one-third of normal. However, with exercise, the limitation of membrane diffusing capacity for oxygen, together with an increase in the rate of passage of red cells through the pulmonary capillaries, will lead to incomplete equilibrium between alveolar gas and end-capillary blood and hence to severe arterial anoxia. It must not be assumed, however, that the entire alveolar-arterial gradient results from a defect in diffusion. In advanced cases, there are often abnormalities in the distribution of both inspired gas and of pulmonary capillary blood flow with increased venous admixture and dead space ventilation.

These anomalies in ventilation-perfusion relationships are more prominent with inflammatory or cellular lesions compared with more chronic fibrotic processes. In the former, single breath tests of [illegible] almost always [illegible] alveolar gas. However, partly because of hyperventilation, the index of intrapulmonary mixing obtained after breathing oxygen for seven minutes is usually normal. Pulmonary

arterial hypertension at rest or on exercise is related to a reduction in the pulmonary vascular bed and ultimately leads to fatal right heart failure.

The outstanding abnormality in pulmonary function is reduction in the diffusing capacity of the lung. Further, if the term alveolar-capillary block is to be applied, a significant defect in diffusion of gases across the alveolar-capillary membrane is, in fact, an essential feature. However, not all of the diseases under discussion consistently lower pulmonary diffusing capacity. Diseases such as sarcoidosis, silicosis and systemic fungus infections, which frequently produce discrete localized nodular lesions as distinct from diffuse disease, may be accompanied by no measurable impairment of diffusion, or at most a slight decrease in diffusing capacity (see Case III, Table 2, Chapter 39) because intervening areas of the lung are relatively normal. Thus, in the face of marked X-ray changes pointing to a diffuse interstitial disease, a relative normal diffusing capacity suggests one of the aforementioned diseases. It should also be emphasized that barium, iron, silver and tin may produce striking diffuse X-ray changes without evidence of impairment of alveolar capillary diffusion or any other abnormality in pulmonary function.

In some instances, the defect in diffusion is overshadowed by the presence of other gross disturbances of pulmonary function. This is particularly true in those relatively acute forms due to infectious or noxious agents, where tests of the mechanics of breathing reveal a marked increase in the resistance of the airways and in which bronchial or bronchiolar damage may be more important than the changes in the alveolar-capillary membrane. Inhalation of chlorine, phosgene, sulphur dioxide, oxides of nitrogen (Silo-Filler's disease) and other irritating gases is more likely to lead to obliterative bronchial disease and to progressive emphysema than to a typical alveolar-capillary block syndrome. In fact, the syndrome described by Austrian and his colleagues is, with exceptions, characteristic only of those diseases with an insidious onset and usually progressive course.

When there is a transient gross defect in diffusion accompanied by even more transient evidence of increased airway resistance, an infectious or immunologic mechanism should be considered. For example, during the acute phase, patients with Farmer's lung show a marked reduction in pulmonary diffusing capacity accompanied by moderate hyperinflation of the lung and evidence of an increased airway resistance. Within two or three weeks, provided additional exposure to moldy forage is avoided, evidence of bronchial or bronchiolar abnormality disappears, and the only abnormality persisting is a defect in pulmonary diffusing capacity. This defect slowly disappears in 3 to 12 months.

The insidious development of a progressive decrease in diffusing capacity and static lung volumes, unaccompanied by evidence of increased airway resistance or gross abnormality in the distribution of inspired gas, is characteristic of diseases such as sarcoidosis, Hamman-Rich syndrome, alveolar cell carcinoma, asbestosis, beryllium disease, talcosis, scleroderma, microlithiasis alveolaris pulmonale, idiopathic diffuse interstitial fibrosis.

Measurements of pulmonary diffusing capacity have been invaluable in demonstrating diseases predominantly affecting the interstitial tissues of the lung. It has been possible to demonstrate abnormality in the alveolar-capillary membrane even before there was significant x-ray change, and to confirm this by lung biopsy. It must be remembered, however, that primary circulatory disorders may also produce a reduction in pulmonary diffusing capacity. Other pulmonary function tests are useful in showing associated abnormalities which, when correlated with clinical and roentgenographic features, limit (often by exclusion) the diagnostic possibilities to a manageable number. In our hands, the measurement of pulmonary diffusing capacity has been one of the most valuable tests of pulmonary function. The measured value for pulmonary diffusing capacity cannot, however, be interpreted correctly without correlation with other available clinical, roentgenographic and physiologic information.

Pulmonary function tests have provided invaluable information concerning the natural history of disease and the effectiveness, or

ineffectiveness, of therapy. Certain diseases are slowly progressive, a few have a natural tendency to improve, while others exhibit a fluctuating course (TABLE 1) Serial tests of pulmonary function provide much more useful information than can be obtained by any single study no matter how extensive. Even diseases with very similar histologic features may show considerable variation in the time course and response to treatment on the part of one or several tests of pulmonary function These variations provide useful diagnostic information in many patients with pulmonary granulomatoses, collagen diseases of the lung and various forms of interstitial pneumonitis Three cases are described at the end of this chapter to illustrate this point Each showed evidence of the alveolar capillary block syndrome due to diffuse pulmonary granulomatosis Case I shows a progressive decrease in pulmonary function due to beryllium disease. Case II shows a fluctuating course characteristic of the patient with pulmonary sarcoidosis treated with corticosteriods. Case III reveals the rapid improvement typical of patients with Farmer's lung Thus, the natural history of the disease as reflected by the course of the pulmonary function tests is of considerable diagnostic importance A progressive decrease in diffusing capacity points to a need for a diagnostic lung biopsy if the etiology has not been established, more vigorous therapy if available, and a guarded prognosis. Unfortunately, many patients with diseases such as sarcoidosis, beryllium disease or Hamman-Rich syndrome may experience symptomatic benefit from the use of corticosteriods, and may show improvement in several pulmonary function tests yet continue to show progressive impairment of diffusion and a relentless downhill course (Case I) Others (Case II), while showing little if any improvement with corticosteriods, relapse when they are discontinued. On the other hand, the granulomatous changes produced by exposure to moldy organic material result in the most marked abnormalities in pulmonary function shortly after exposure Provided further contact is avoided and, depending on the severity of the process, there is striking improvement in pulmonary function after two to four weeks of corticosteriods followed by a more gradual return of diffusing capacity to normal values in 2 to 10 months Repeated attacks, however, may lead to progressive pulmonary fibrosis

Thus, repeated tests of pulmonary function over an extended period of time can provide much more useful information than would be possible with any single study, no matter how extensive.

DIAGNOSTIC TESTS

Because of the wide variety of diseases with diverse etiologies encountered, a fairly systematic study is usually necessary in order to arrive at the proper diagnosis. The use of fungus and tuberculin skin tests, complement fixation studies for histoplasmosis, blastomycosis and coccidioidomycosis, and cultures for fungi and tubercle bacilli may establish a diagnosis of miliary tuberculosis or a disseminated fungus infection

Skin and muscle biopsies or the demonstration of the characteristic LE cells may lead to a diagnosis of pulmonary scleroderma, polyarteritis nodosa, or disseminated lupus erythematosus. The Kveim test for sarcoidosis[25] and beryllium patch test[3] are occasionally helpful The sputum should also be examined for the presence of malignant cells, eosinophiles, hemosiderin in the macrophages, and asbestos bodies in order to establish a probable diagnosis of alveolar cell carcinoma, eosinophilic pneumonitis, primary pulmonary hemosiderosis or asbestosis

Scalene Node Biopsy

Of the more direct diagnostic methods, scalene node biopsy[9] is frequently helpful In the presence of hilar adenopathy, there is a high incidence of abnormality in the scalene nodes and the biopsy is frequently diagnostic in patients with sarcoidosis, lymphogenous carcinomatoses, lymphomas and infectious granulomas. If lymphoid tissue is obtained, it will show granulomatous lesions in the majority of patients with pulmonary sarcoidosis. Conversely, failure to find this type of reaction in the scalene lymph nodes is strong presumptive evidence against a diagnosis of sarcoidosis. In patients with Farmer's lung and most of the

chronic forms of interstitial fibrosis, biopsy of the scalene lymph nodes is not helpful

Lung Biopsy

If the scalene lymph nodes have not revealed any diagnostic histologic abnormality or the disease suspected is one in which this method is rarely diagnostic, serious consideration should be given to obtaining a small portion of the lung for microscopic study [22] As the process is usually diffuse, any part of the lung should show the characteristic lesions Therefore, the surgeon can perform a limited thoracotomy and remove a small wedge of lung (e.g , the tip of the lingula) as it presents itself in the incision Unless the patient has severe pulmonary insufficiency, this procedure is well tolerated. It is neither necessary nor particularly helpful to do an extensive exploratory thoracotomy Alternatively, if pleural adhesions are present, a needle biopsy may be attempted, but if the pleural surfaces are not adherent, the risk of pneumothorax or hemorrhage makes limited thoracotomy a safer procedure.

Although lung tissue is available for microscopic examination, the etiologic diagnosis may remain in doubt Even when the characteristic microscopic appearances of sarcoidosis are present, it is advisable to eliminate the possibility of infectious granulomas by stains for fungi and acid-fast organisms as well as by appropriate cultures of the tissue If there is a history of possible exposure to beryllium, a spectrographic analysis of the tissue for beryllium is warranted. The histologic features of the peculiar granulomatous lesion of Farmer's lung are quite characteristic. The finding of asbestos bodies in the parenchyma or pleura will identify asbestos as the cause of pulmonary fibrosis. Silicosis may also be recognized by the microscopic features; however, the biopsy specimen is usually too small to permit accurate chemical analysis for silica

In spite of all diagnostic studies the etiology of many of the diffuse interstitial fibrosis of the lung remains obscure With additional experience, it is probable that more accurate diagnosis will be possible, especially if the biopsy material is obtained relatively early in the disease. The importance of early biopsy should be emphasized. It is known, for example, that sarcoidosis leads to a fibrous reaction in the lung which eventually loses all the original granulomatous characteristics although earlier lymph node biopsies have been quite characteristic.

Treatment for most of the interstitial diseases is unsatisfactory Oxygen is usually beneficial in the acutely ill patient The exact role of corticosteriods in therapy is still uncertain In acute pulmonary reactions to noxious agents, corticosteriods should be used On the other hand, these drugs may do more harm than good in the acute diseases of viral etiology. Granulomatous reactions appear to respond favorably However, the possibility of activation of unrecognized tuberculosis or fungus infections must be kept in mind Antibiotics may be useful if there is bronchitis or bronchiectasis accompanied by the production of purulent sputum If hypersensitivity plays a role, as it appears to do in patients with Farmer's lung, the patient will benefit most from removal of the offending material. Corticosteroids may be useful in the acute episodes of this disease In beryllium poisoning, corticosteroids result in considerable improvement in the roentgen picture but pulmonary function studies have revealed a steady decline in spite of continued therapy [16, 21]

Conclusion

The diffuse interstitial diseases of the lung present a challenge to the clinician and investigator alike. Their identification requires the combined efforts of the internist, chest physician, surgeon, pathologist, radiologist, physiologist and chemist Three cases have been selected to demonstrate the variability of the natural history of these disorders and to stress clinical utility of longitudinal testing of pulmonary function.

Case I Beryllium Poisoning

A 34 year old man was well until the spring of 1956, when he noted the gradual onset of shortness of breath on exertion He consulted his physician, who was unable to find any abnormality on physical or electrocardiographic examination In November, 1956, he went deer hunting as he had done for several years



FIG 1—(A) *Case I* There are patchy mottled densities in both lung fields along with accentuation of linear markings The left lung is more seriously involved than the right, although this is somewhat obscured by the pleural reaction from the recent lung biopsy. The high diaphragms indicate inability to fully expand the lungs (Courtesy of Dr John H Juhl)

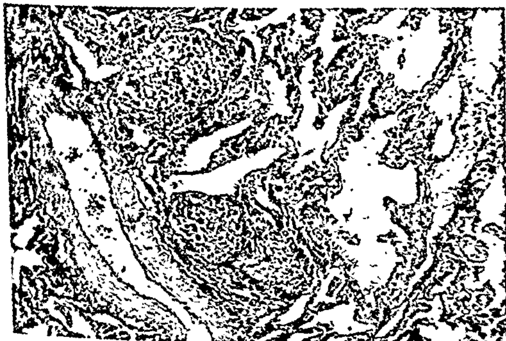


FIG 1—(B) *Case I* (x-150) A blood vessel with two closely positioned noncaseous nodules composed of epithelioid cells, scattered lymphocytes, a few vacuolated histiocytes and several multinucleated giant cells The alveolar septae are thickened and there is some interstitial fibrosis (Courtesy of Dr Walter H Jaeschke)

When he attempted to drag the deer to camp, he became extremely short of breath and felt as though he were dying. His companion helped him back to camp. After about one week he felt quite well although he remained dyspneic on exertion. In a heavy snow fall in March, 1957, he experienced another similar and frightening episode of dyspnea after walking about one block through deep snow. He was hospitalized and a chest roentgenogram was found to be abnormal. A probable diagnosis of Boeck's sarcoid was made, and he was placed on corticosteroid therapy. In the latter part of May, he had another acute episode of breathlessness while fishing. Because he was noted to be cyanotic, he received oxygen therapy with marked relief of symptoms. He was admitted to the University Hospitals on June 11, 1957. Occupational history revealed that he had worked as a tumbling barrel operator with a copper beryllium alloy reported to contain "considerably less than 3 per cent beryllium" in the period from March, 1954, to March, 1955.

The physical examination showed evidence of an old burn scar of the right arm and right chest. Motion of the thoracic cage was reduced. Breath sounds were bronchovesicular over the left anterior lower chest and right lower chest posteriorly, post-tussive rales were prominent in these areas. There was slight clubbing of the fingers. Urinalysis, complete blood count, serum proteins, calcium and phosphorus were all within normal limits. An electrocardiogram was normal. Postero-anterior and left lateral chest roentgenograms showed patchy mottling throughout much of the left lung with lesser involvement on the right. The left hilar lymph nodes were slightly enlarged. There was no evidence of pleural disease. Pulmonary function studies revealed the characteristic features of the alveolar-capillary block syndrome. On June 11, 1957, a surgical biopsy of the lingular area was carried out. The lung was described by the surgeon as "feeling hard, indurated, and hobnailed on palpation." The microscopic section was interpreted as follows:

The parenchyma contains single nodules and conglomerate masses made up of nodules which show no evidence of caseation or necrosis. The nodules have epithelioid cells, with multinucleated giant cells, most of them of the foreign body type with nuclei in the central portion. There is fibrous tissue surround- [illegible] tions of macrophages.

The remaining tissue was submitted for analysis. Beryllium was detected spectrographically (9 μg/0.5 Gm. of wet lung tissue).* The postoperative course was uneventful, and he was subsequently given large doses of corticosteroids with temporary symptomatic relief but no objective improvement. Because of the development of hypertension and other evidence of hypercortisonism, it was necessary to decrease the dose of corticosteroids.

* Since only a very small portion of lung tissue was available for chemical assay, there is some uncertainty concerning the accuracy of the quantitative determination.

Comment

The initial pulmonary tests were characteristic of the aveolar-capillary block syndrome (Table 5). The static lung volumes were reduced and the residual volume/total lung capacity was relatively normal. Maximum breathing capacity, timed vital capacity and maximum respiratory flow rates were relatively well preserved. The distribution of inspired gas was normal by the 7 minute wash-out of nitrogen, and only slightly abnormal by the single breath test. There was hyperventilation, a relatively normal arterial saturation and reduced arterial carbon dioxide tension at rest. Pulmonary diffusing capacity was markedly reduced. Additional studies (not shown in Table 5) revealed a fall in arterial saturation of 6.3 per cent with exercise, an increase in the resting physiologic dead space to 227 ml. and an increase in resting dead space/tidal ventilation to 43.8 per cent. At the time of the initial studies, he had received no corticosteroids for over a month. After reinstituting treatment with these drugs, there was partial relief of symptoms but no objective improvement in pulmonary function tests.

This patient exemplifies the progressive course uninfluenced by therapy often seen in patients with diseases that appear insidiously and progress slowly (Table 1, *13–24*).

Case II: Boeck's Sarcoid

A 43 year old white woman was seen at the University Hospitals on January 29, 1953. She had been well until the fall of 1952, when she noted a chronic nonproductive cough accompanied by progressive fatigue. In August, 1953, following a chest roentgenogram she was admitted to a sanatorium. Previous chest x-rays in 1948, 1949 and 1950 had been normal. All attempts to recover tubercle bacilli had failed and she was referred to the hospital for evaluation.

Physical examination revealed only a few rales in the right midlung area. Urinalysis and blood count were normal. Serum albumin was 4.3 Gm. and globulin 3.3 Gm./100 ml. Bone marrow aspiration, a culture for fungi of the marrow aspirate, and bronchoscopy

TABLE 5 —*Physiologic Features Demonstrated Over a Period of About 2 Years by a 3½ Year Old White Male Suffering from Diffuse Pulmonary Granulomatosis Caused by the Inhalation of Beryllium*

Test	Normal	6/11/57	4/3/58	5/11/59
LUNG VOLUMES				
Vital capacity (L)	4 01	1 59	1 56	1 13
Residual volume (L)	1 23	0 60	0 60	0.50
Functional residual capacity (L)	2 04	1 22	1 15	1 03
Total lung capacity (L)	5 28	2 22	2 16	1 83
Residual volume/total lung capacity × 100 (%)	23 3	27 2	27 8	32 3
MECHANICS OF BREATHING				
Maximum breathing capacity (L /min)	130	80	83	82
[illegible]	82	97	94	93
[illegible]	97	100	100	100
[illegible]	500	362	215	—
Maximal inspiratory flow rate (L /min)	400	232	177	—
DISTRIBUTION OF INSPIRED GAS				
% nitrogen after 7 min on O_2	<2 5	0 5	0 5	0 5
Single breath of oxygen (nonuniformity of alveolar gas)		+	++	+++
ARTERIAL BLOOD GASES				
Oxygen saturation (%)	96	94 6	91 1	89 4
Carbon dioxide tension (mm Hg)	40	36	32	38
pH	7 4	7 48	7 54	7 42
Hemoglobin	14 5	16 5	15 8	16 3
VENTILATION				
Respiratory rate/min	14	20	22	19
Tidal volume (ml.)	550	560	530	590
Respiratory minute volume (L /min)	6 0	11 2	11 5	11 0
DIFFUSION				
Diffusing capacity for carbon monoxide (ml /min /mm Hg)	29 4	7 3	7 4	5 7

were *normal* Chest roentgenograms showed widespread nodular densities throughout the midlung fields The right lung was more involved than the left. There was evidence of bilateral hilar adenopathy A Supraclavicular lymph node was removed and the microscopic section revealed a granulomatous lesion consistent with sarcoidosis. Because of increasing cough and wheezing, bronchoscopy was repeated in October, 1954, and again considered to be *normal* At this time, the chest x-ray showed increase in the nodular densities and the right pleura was thickened. Because of the pleural changes, a lung biopsy was deemed advisable to rule out the possibility of an unusual fungus infection The surgeon reported that the pleural surfaces were adherent, and that the lung was firm and nodular in consistency A portion of lung was removed from a very firm nodular area in the middle lobe The microscopic section showed irregular dense fibrous foc[illegible]

epithelioid [illegible]

clear phag[illegible]

sizes Cult[illegible]s of the resected tissue for fungi and tubercle bacilli showed no growth

After these reports were available, the patient was given hydrocortisone and later prednisone In March, 1958, she was gradually taken off all corticosteroids. The chest x-ray had cleared considerably over this period of time, and the patient had improved symptomatically On April 24, 1958, the progress chest x-ray suggested an increase of the fine nodular densities especially in the left lung Pulmonary function studies on May 9, 1958 (TABLE 6) likewise revealed evidence of worsening On July 23, 1958, there was again evidence of slight increase in the disease roentgenographically and further decrease in her pulmonary function She was then started on triamcinolone and maintained on 2 mg twice a day. When seen again on May 1, 1959, the chest x-ray had cleared considerably and was similar to the film taken before the exacerbation

Comment

The original pulmonary function tests performed on this patient (TABLE 6) revealed evidence of a slight to moderate alveolar-capillary block syndrome. Compared with Case I (TABLE 5) there was less abnormality in diffusing capacity but more abnormality in the distribution of inspired gas. Withdrawal of corticosteroids produced a slight but significant



Fig 2—(A) *Case II* There is a minimal amount of hilar adenopathy Numerous small discrete nodules are noted bilaterally Some conglomeration is noted *on the right and the density is accentuated by slight* pleural thickening, probably secondary to thoracotomy The distribution is somewhat more asymmetric than is usually observed in sarcoidosis (Courtesy of Dr John H Juhl)



[illegible] composed of some fibrous tis-

(Courtesy of Dr. Walter H Jaeschke)

TABLE 6—*Physiologic Features Demonstrated Over a Period of About 2 Years by a 43 Year Old White Female Suffering from Pulmonary Granulomatosis Due to Sarcoidosis*

Test	Normal	7/31/57	5/9/58	7/23/58	12/3/58	5/1/59
LUNG VOLUMES						
Vital capacity (L)	2 81	2 48	2 22	1 68	2 11	2 26
Residual volume (L)	0 86	2 02	1 32	0 97	1 19	1 35
Functional residual capacity (L)	1 56	2 82	1 98	1.37	1 49	1 71
Total lung capacity (L)	3 66	4 56	3 55	2 78	3 34	3 59
Residual volume/total lung capacity × 100 (%)	23 4	44 2	37 1	32 5	35 7	37 6
MECHANICS OF BREATHING						
Maximum breathing capacity (L/min)	79	73	63	58	71	72
% vital capacity in 1 sec	83	70	68	68	68	67
% vital capacity in 3 sec	97	98	88	93	89	89
Maximal expiratory flow rate L/min	350	—	—	185	237	—
Maximal inspiratory flow rate L/min	300	—	—	192	228	—
DISTRIBUTION OF INSPIRED GAS						
% nitrogen after 7 min on O_2	<2 5	3 1	2 0	1 5	2 6	2 8
Single breath of oxygen (nonuniformity of alveolar gas)	—	+	++	+++	++	++
ARTERIAL BLOOD GASES						
Oxygen saturation (%)	96	94 0	93 7	92.3	93 1	—
Carbon dioxide tension (mm Hg)	40	40	35	—	—	—
pH	7 4	7 40	7 41	—	—	—
Hemoglobin	14 5	12 3	13 2	12 6	14 2	—
VENTILATION						
Respiratory rate/min.	12	9	13	16	11	12
Tidal volume (ml)	400	780	544	390	432	434
Respiratory minute volume (L/min)	5	6 7	7 3	6 3	4 8	5 3
DIFFUSION						
Diffusing capacity for CO (ml/min./mm Hg)	24 0	—	20 2	16 0	19 8	20 3

decrease in static lung volumes after one month, and a very definite decrease in static lung volumes, diffusing capacity and mechanics of breathing after three months Reinstitution of corticosteroids restored most pulmonary function tests to their original value Although corticosteroids were not curative, they were apparently capable of maintaining the status quo Definite relapse followed their withdrawal. It is uncertain how long therapy will have to be maintained. This patient exemplifies the fluctuating course seen in certain diseases. (TABLE 1, *9–12, 17*)

Case III Farmer's Lung

On November 26, 1957, a 48 year old man was seen because of shortness of breath He dated the onset of this difficulty to mid Septe...

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of "white mold" especially at the edges He worked throwing this dry moldy silage down a chute from about 1:00 p m to about 2:30 p m By 4:00 or 4.30 p m he felt ill and by 5:30 p m he had a severe headache and vomited Following this he felt feverish, and coughed almost continuously During the night he continued to suffer from a hacking cough and high fever By next morning he was somewhat better but some general symptoms continued for several weeks Both he and his wife estimated it was three months before he returne...

worked from about 1 to 2 p m By 4 p m he developed headache, vomiting, and severe coughing A few hours later a very high fever ensued together with severe shortness of breath After 10 days he felt much improved, but was still short of breath on any physical exercise On November 20, 1957, he again worked in the silo for about one-half hour and was much more short of breath that evening.

Physical abnormalities were restricted to the



FIG 3—(A) *Case III* There is diffuse accentuatio of the linear markings at the bases associated with reticular pattern of the peripheral interstitial struc tures (Courtesy of Dr John H Juhl)



FIG 3—(B) *Case III* (x-150) Two fairly well defined tubercles with some organizing pneumonitis and thickening of adjacent alveolar walls typical of Farmer's lung (Courtesy of Dr. Walter H Jaeschke)

TABLE 7.—*Physiological Features Demonstrated Over a Period of About 1 Year by a 48 Year Old Farmer Suffering from Pulmonary Granulomatosis Which Resulted from Exposure to Moldy Silage (Farmer's Lung)*

Test	Normal	11/26/57	12/19/57	10/17/58
LUNG VOLUMES				
Vital capacity (L.)	4.01	3 22	4 05	4.40
Residual volume (L.)	1 22	3.23	1 01	0 97
Functional residual capacity (L.)	2 03	4 81	3 10	3 09
Total lung capacity (L.)	5 23	6 55	5 27	5 77
Residual volume/total lung capacity × 100 (%)	23 4	49 4	19 1	16 9
MECHANICS OF BREATHING				
Maximum breathing capacity (L./min.)	121	99	126	144
% vital capacity in 1 sec	83	76	98	89
% vital capacity in 3 sec	97	92	100	100
Maximal expiratory flow rate (L./min.)	500	310	454	421
Maximal inspiratory flow rate (L./min.)	400	237	312	388
DISTRIBUTION OF INSPIRED GAS				
% nitrogen after 7 min. on O_2	<2 5	1 0	1 0	1.4
Single breath of oxygen (nonuniformity of alveolar gas)	—	++	+	+
ARTERIAL BLOOD GASES				
Oxygen saturation (%)	96	88 9	95 6	94 9
Carbon dioxide tension (mm. Hg)	40	36	39	—
pH	7 4	7 40	7 39	—
Hemoglobin	14 5	13.5	13 2	13.1
VENTILATION				
Respiratory rate/min.	14	20	24	21
Tidal volume (ml.)	500	630	472	470
Respiratory minute volume (L./min.)	6	12.4	11 5	9.7
DIFFUSION				
Diffusing capacity for carbon monoxide (ml./min./mm. Hg)	30 7	12 1	14 0	19 4

lungs. There was no wheezing, but there were numerous subcrepitant rales at the height of *inspiration* throughout the lower one half of both lungs. Chest roentgenograms revealed fine linear striations and granular changes in the lower lobes. Pulmonary func- [illegible] clinical improvement. The dose of corticosteroids was gradually reduced and finally all treatment stopped in April 1958. By avoiding moldy material, and when [illegible] nt filter mask without any [illegible]

Comment

Physiologic studies (TABLE 7) revealed a significant decrease in both diffusing capacity and vital capacity. Unlike the *previous* 2 cases, however, there was an increase in residual volume, total lung capacity and residual volume/total lung capacity. Alveolar gas was nonuniform, and there was evidence of abnormality in ventilation/bloodflow relationships, since the reduction in arterial saturation could not be explained by the decrease in diffusing capacity alone. Within a month there was marked improvement in all ventilatory tests. The diffusing capacity frequently takes several months gradually returning to normal. This patient exemplifies the acute onset of maximum disability followed by moderate or rapid improvement characteristic of many patients with acute forms of interstitial pneumonitis (TABLE 1, *1–8*).

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groundwork of cor pulmonale may be laid. This is a serious problem in atelectasis of the whole lung rather than in lobar or segmental atelectasis, and especially in patients with coexisting emphysema.

On physiologic grounds, therefore, the ideal situation in therapy is to re-expand atelectatic alveoli and restore lost ventilation and circulation; unfortunately, this is not always possible due to associated anatomic pathology. In the remainder of the lung, there is an inevitable compensatory emphysema. This results in alveolar stretching, i.e., expansion, into the space of the thorax. Although in the young person this can be done with only a minimal loss of mechanical efficiency of breathing, in the older person this may result in actual damage to the elastic structures in the alveoli, and, therefore, a secondary mechanical defect may develop in which the alveoli do not recoil in a normal manner. This adds, then, a typical expiratory difficulty to the already restricted ventilation.

Pulmonary Fibrosis

In fibrosis of the lung, not only is there loss of alveoli with the resulting ventilatory and circulatory disturbance, but due to the presence of the fibrosis itself a second vascular abnormality may occur. This consists of an increase in the bronchial circulation to the part of the lung involved. The bronchial artery essentially is a systemic system and, therefore, at a higher pressure than the pulmonary system. As the inflammatory process becomes *fibrotic*, a series of anastomoses commonly develop between the bronchial and the pulmonary arterial systems with the result that bronchial artery blood flows into the pulmonary circuit.[15] The effect of this is to put higher pressure blood into a lower pressure system and thus raise the pressure in the pulmonary artery, increasing the work of the right ventricle. Thus, in pulmonary fibrosis, a pulmonary hypertension beyond that usually expected in alveolar destruction is a common finding, and cor pulmonale becomes a far more important process than it does with atelectasis alone. Nakamura[14] Czudkowitz[8] and Liebow[13] have shown independently that severe pulmonary fibrosis may result in a considerable part of the output of the left heart being shunted into the pulmonary capillary bed and thus recirculating. The consequence of this is increased work for the left ventricle as well as the right and in certain cases, left heart failure may develop terminally.

Pulmonary fibrosis is seldom so anatomically localized as atelectasis. Usually, it is scattered throughout a lobe, a lung or both lungs. The consequences of this are not only loss of volume due to alveolar destruction and scar formation but also localized distortion of adjacent normal alveoli with loss of function. The lung as a whole becomes stiffened. The stiffening of the lung acts not only as a mechanical bar to adequate ventilation but also will cause changes in the Hering-Breuer and intercostal reflexes which control rate and depth of respiration to a considerable extent. It is clear that the effects of pulmonary fibrosis are profound and that its therapy must be most difficult since it is commonly not specifically localized.

Pulmonary Destruction

This is seen either in atelectasis with giant cavity formation or in tuberculosis disseminating by lymphatic or hematogenous routes. In the first case, the physiologic result is a combination of atelectasis and fibrosis; in the second case, as the result of treatment, there may be healing of the process without considerable fibrosis. The effects of the latter condition are to stiffen the lungs somewhat, to reduce its volume eventually by alveolar destruction and so to cause alveolar loss both from the ventilatory and circulatory point of view with some compensatory emphysema of mild degree. During the active phase of the disease, the physiologic status may be of considerable theoretical interest with thickening of the alveolar membrane[5] and thus a bar to oxygen transport as well as reflex changes, causing a total increase in CO_2 excretion due to hyperventilation.

Pleural Fibrosis

This occurs either as the result of pleural inflammatory disease with or without ef-

restriction of ventilation by a simple mechanical process. Ventilation of the affected lung is

Physiologic Sequelae of Pulmonary Tuberculosis

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THE worldwide decline in prevalence of pulmonary tuberculosis has allowed us to pay more attention to the late effects of the disease than had been possible in earlier periods The advent of chemotherapy, moreover, has resulted not only in an increased number of patients with recognizable and often serious pulmonary damage in whom the infectious disease itself has been arrested, but also has brought to the fore surgical considerations in the disease These in themselves may modify physiologic function The physiologic problems of tuberculosis are not specific for that disease, yet the need for physiologic consideration in a large number of patients is such that separate consideration of the results of tuberculosis is justifiable Today, the clinical pattern of the disease has changed such that two groups of patients comprise the majority that we are seeing in the U S those with serious pulmonary damage and consequent physiologic disturbance, and patients with limited disease which can be controlled and thus avoid pulmonary dysfunction However, the more classic forms are still seen frequently in some parts of the world and still require discussion

Results of Tuberculosis

Physiopathologically, the effects of pulmonary tuberculosis may be tabulated as·

1 Parenchymal destruction with loss of pulmonary volume and vascular bed
   a atelectasis
   b pulmonary fibrosis
   c simple destruction without considerable fibrosis
2. Pleural fibrosis with adhesion.
3. Bronchial abnormalities
   a. stenosis
   b bronchiectasis.

Although the physiologic difficulties produced by these various phenomena are similar in some respects, the underlying principles may be quite different Therefore, it is worth considering these separately As well we must consider the possible physiologic effects of therapy.

Atelectasis

Obviously, atelectasis removes a group of alveoli from ventilation. Reduction in the volume of the affected area will cause a compensatory emphysema of the rest of the lung At the same time, there may be a loss of mechanical efficiency due to this compensatory emphysema Thus, there is a net loss as a rule in the timed vital capacity and in the maximal breathing capacity When the atelectasis is extensive enough, we will therefore have a patient who is short of breath because of mechanical interference with ventilatory function in remaining lung as well as because of loss of important areas of alveolar structure

Atelectasis is also associated with abnormalities of the pulmonary circulation. It was shown by Berggren[3] in 1942 that if there is low oxygen tension in the alveolus, such as would be present in a nonventilating atelectatic area, a chemical reflex will cut off the pulmonary arterial blood flow into the capillaries It is for this reason that a patient with pure atelectasis is rarely cyanosed since blood does not pass through these nonventilating alveoli The disadvantage to the patient is that the output from the right heart has to pass through a smaller vascular bed than normal. When atelectasis is extensive enough and particularly when other disease processes are present in the rest of the lung, the work of the right ventricle and thus the pulmonary artery pressure must rise to fulfill the needs of a cardiac output. In this way, the

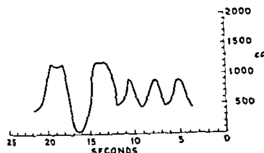


Fig 1—A characteristic spirogram of fibrosis and pleural stiffening

The slowing of expiration, as a rule, is relatively more uniform in pulmonary fibrosis or destruction This is well shown in Figure I, a characteristic spirogram of fibrosis and pleural stiffening However, in many cases, the typical emphysematous increasing expiratory lag may be seen This is demonstrated in Case I (Figs. 2 and 3).

Because of the enlarged alveoli in the emphysematous area, and because of the increased dead space[10] so often found (particularly in fibrosis), there is usually hyperventilation at rest and on effort. Arterial oxygen desaturation on exercise is a common finding More detailed study may show marked defects of gas mixing,[6] and an increase in the ratio of the residual air to the total lung capacity [12] Changes in acid-base balance are perhaps less common, and vary when present. Serial study of the patient may show that chest wall retraction may be beneficial in taking up space, but that the bellows mechanism is impeded by the scoliosis produced

Destruction of Lung Tissue and Resultant Retraction: Treatment

"Active" Cases

Ideally, surgical collapse therapy should be instituted when the retraction is stabilized, and this may well be combined with resection. However, one must remember that either of these two procedures may introduce further physiologic problems [4]

The major effort in the treatment of active cases, from a physiologic point of view, is the prevention of emphysema If there has been any substantial reduction in lung volume, space take-up, usually by some degree of surgical collapse, is standard procedure at the present time for adults. In children, space take-up is ordinarily avoided. Very young children may form new alveoli after a resection and older children will ordinarily compensate for the reduced volume without the development of a permanent emphysema. However, physical therapy[17] is necessary in order to avoid gross distortion of the chest; in most cases, such therapy will be perfectly adequate to maintain normal chest form, mobility and function. The effects of surgical space take-up, such as a thoracoplasty, are far too inimical to normal growth to use indiscretely during the growing period.

When emphysema has become irreversible,



Fig 2—(*Case I*) X-ray of a 35 year old female showing a long-standing pulmonary fibrosis in the left lower lung There is marked elevation of the left diaphragm Compensatory emphysema of the left upper lung field is demonstrated by an increased radiolucency.

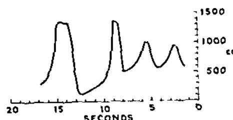


Fig 3—(*Case I, concluded*) A spirogram showing marked diminution of the vital capacity. Expiration

reduced because of encasement of the lung within the unyielding pleura. The peripheral alveoli, of course, are affected most and those nearer the hilum least, since mediastinal movement may permit their ventilation Such rigid alveoli will have a lower oxygen content than normal, and blood passing through them will not be fully oxygenated nor will carbon dioxide be excreted so well Since the respiratory center will respond to any increase in arterial carbon dioxide tension, the other lung takes over and increases ventilation. The results then are ventilatory restriction and hypoxia with normal carbon dioxide levels in the arterial blood

When pleural adhesions, particularly vascular ones, are involved, anastomotic channels between the intercostal vessels and the pulmonary vein may develop, the direction of flow will depend on the pressure in the two systems. In cor pulmonale, with rise to systemic venous pressure, blood will bypass the right side of the heart. This increases the load on the left heart without affecting the right ventricle and pulmonary artery. Such a situation is seen particularly following bilateral thoracoplasty and is a cause of left ventricular failure appearing as a terminal event.

Bronchial Abnormality

Bronchostenosis may effect pulmonary function to a greater extent than is often realized. Absolute bronchostenosis produces classical atelectasis. In lesser degrees of bronchostenosis, the airway is impeded to the affected part of the lung Since bronchi narrow in expiration, deflation of the affected part of the lung will be more affected than inflation except in very minor degrees of bronchial narrowing The classic appearance of obstructive emphysema in a very nearly complete bronchostenosis is well known. It is often not realized that this still must be considered even when the obstruction is not so great, the result being inflation of a part of the lung without hyperinflation Such lung does not become oxygenated and therefore behaves in many respects as atelectatic lung, cutting off its own blood supply. This is best detected by a combination of inspiration-expiration x-ray films together with careful fluoroscopy. In certain cases, it may be necessary to do more elaborate procedures such as bronchospirometry to prove the existence of this condition

Bronchiectasis is a concomitant of tuberculous lesions both because of the alveolar destruction and the bronchial inflammation. The effects of bronchiectasis are seen not only in the contiguous atelectasis from retained secretions, but also in the increased bronchial artery-pulmonary artery anastomotic channels that can develop Thus, it acts as an exacerbator of the more primary parenchymal disease already described

Destruction of Lung Tissue and Resultant Retraction Appearance

Clinical

The main findings in a patient with marked pulmonary fibrosis or destruction of the lung are dyspnea and cyanosis, especially on effort. These manifestations vary with extent of the underlying pathologic condition, and may be modified by the amount of activity of the patient at the time of observation. So often one underestimates dyspnea in bed patients or may be surprised by such a patient's poor tolerance of exercise Patients often complain of exertional dyspnea, and one may notice, on spirography, that they tend to be tachypneic. Clinically and radiologically, we frequently find signs of associated emphysema [9] In cases of fibrosis we may find localized bullae, sometimes indistinguishable in radiologic appearance from tuberculous cavities In the case of lobar destruction, there is almost invariably some associated compensatory emphysema of the other lobe. We also may notice changes in the chest wall and elevation of the diaphragm, appearing slowly and often becoming major factors causing scoliosis and inefficiency of the bellows apparatus on the other side.

Function Studies

Pulmonary function studies[7] may show diminished vital capacity and slowing of both expiration and inspiration One can often differentiate pulmonary fibrosis or destruction from obstructive emphysema by the much greater slowing of inspiration than expiration.

merely to point out the necessity of the adequate physiologic evaluation which must precede surgery.

Effects of Surgery

The complications of lung surgery vary with the type of operation, but problems of atelectasis, pleural or extrapleural accumulation of fluid, with resulting compression of the lung, postoperative infection, and so forth, are seen not infrequently following major pulmonary surgery. Also, in some form of alteration of the rib cage, such as in thoracoplasty, the mechanical changes which result may impair pulmonary reserve. Such untoward developments should be anticipated, since their effects on the postoperative course of the patient may be considerably reduced by preoperative therapy.

For this reason, along with the evaluation of the patient's pulmonary reserve, it is essential to start a program of breathing, coughing and postural exercises which, if regularly practiced, will materially reduce the effects of whatever complications may develop. This phase of therapy has been understressed in the past. We regard it as of such importance that *surgery should be delayed until the patient has had adequate training and practice* under the guidance of a physician with special experience in this field. Such matters as deep breathing exercises, intermittent positive pressure therapy to reduce sputum and improve expectoration, and postural exercises with the mirror at the foot of the bed should be the routine preoperative training for each patient. Sputum should be reduced to a minimum by using antibiotics that will combat any concomitant infection.

The Operative Phase

The actual operative phase is under control of the trained anesthetist who understands and applies known physiologic principles.[2] Facilities for careful following of ventilation may not be available in every hospital. When any question of acidosis exists, it is exceedingly important to maintain adequate ventilation throughout the operation. Since pure oxygen is commonly used during surgery, arterial oxygen desaturation may not be a sufficient guide to adequate aeration. Ideally, the anesthetist should be able to study the carbon dioxide content of expired air continually throughout the operation, using an automatic analyzer. When this is not possible, and the operation is prolonged, it is desirable to have facilities for a blood pH available to the anesthetist. Although a large tidal volume may create difficulties surgically, it is often better to have a large tidal volume and to slow the procedure than it is to use a small tidal volume and operate more rapidly.

The immediate postoperative phase, particularly if the patient does not recover consciousness rapidly after the operation, presents further problems. Since commonly the patient may be hypopneic during this phase, acidosis may develop as a result of carbon dioxide retention.[13] Until the patient fully recovers consciousness, some attention should be paid to this, with intermittent positive pressure breathing through a laryngeal tube instituted as needed. Alkalosis, by and large, is a much less serious proposition to treat than acidosis, it is also easier to diagnose.

The Postoperative Phase

Upon the recovery of consciousness, again, hypopnea may result from pain and discomfort. As soon as consciousness is recovered deep breathing exercises with coughing should be instituted. When there is any question of inadequacy, intermittent positive pressure or a cough machine should be utilized. Opiates and other drugs depressing respiration should be used sparingly. When the integrity of the thoracic cage has been altered, as in thoracoplasty, some stabilization of the affected area should be instituted in order to control any paradoxical respiration that may develop. A physical therapist with a sound background in pulmonary physiology is a great asset to a thoracic surgical unit.[17] By these means many complications of thoracic surgery can be avoided.

Surgical Procedures

The various surgical procedures used in pulmonary tuberculosis are briefly discussed here. For more detailed discussion of the

the case must be treated as chronic, with especial attention to preventing further disability. In such patients, breathing exercises[1] may contribute much to maintaining pulmonary function, together with other therapeutic measures aimed specifically in this direction.

"Chronic" Cases

As with most other progressive disease processes, the distinction between "acute" and "chronic" in tuberculosis is likely to be a matter of opinion. From the physiologic considerations, the most useful criterion is the respiratory status of the patient. *From this point of view*, a case of tuberculosis may be regarded as chronic when pulmonary destruction and fibrosis, together with secondary abnormalities such as emphysema, are so extensive as to result in some degree of respiratory disability.

When possible, chronic tuberculosis is treated by excisional surgery. However, many patients are not suitable candidates since their fibrosis is far too extensive, or there is other pulmonary disease. Physiologic disability may be too great or the patient may decline surgery. In such cases, the management becomes infinitely more difficult. In patients who are not treated surgically, the physician must be concerned with the physiologic improvement of the patient so far as is possible, together with antimicrobial therapy for tuberculosis.

The basis of management of such a patient includes a regimen of carefully planned breathing exercises[1] to train the patient to make maximum use of the normal pulmonary tissues. Of greater importance is the control of secondary bronchial infections with chemotherapy and other measures. In some cases, intermittent positive pressure breathing[19] with bronchodilators may be of great value. This is particularly true in long-standing fibroid tuberculosis with emphysema and retained bronchial secretions. Even slight improvement in patients who are seriously short of breath may make a great difference to the patient's life; a 5 per cent improvement of pulmonary reserve may make the difference between discomfort and reasonable comfort at rest or on mild effort.

Surgical Measures

Some kind of surgery is usually planned for the majority of tuberculosis patients at the present time. Removal of a destroyed lobe, in the presence of disease on the other side, often becomes possible after sufficient therapy has rendered the contralateral disease quiescent. Conversely, it may be desirable to eradicate a major focus of disease in the hope that lesser foci will become quiescent as a result.

Physiologic Considerations in Surgery for Tuberculosis

The advent of antimicrobial *therapy* has reoriented our thinking toward resection, when possible, of damaged tissue or potential foci of reactivation of the disease. Yet, resection carries more risk than other procedures, and often a less definitive approach has to be adopted. When removal of a destroyed lobe is under consideration, little harm can result from an uncomplicated resection from the physiologic point of view, if space take-up is adequate and the mechanical efficiency of the bellows mechanism of the lung is not impaired.

The physiologic evaluation of patients before surgery is of the greatest importance. Some knowledge of the kind of pulmonary function which can be expected postoperatively is essential, both in the event the operation is a complete success and in case of operative modifications *or complications*. That is to say, resection of an upper lobe that is destroyed in a patient with considerable fibrotic disease on the other side cannot be considered in terms of a successful resection alone. The contribution of the rest of the lung on the side where resection is planned to the over-all pulmonary function may be exceedingly important to know, since, if the patient should develop a bronchopleural fistula, empyema or a pleural effusion with later pleural fibrosis, the best functioning unit of the lungs may be lost. Again, it is not infrequent that an operation intended to be a lobectomy, may present such technical difficulties, together with disease unsuspected prior to surgery, that a more extensive resection has to be done. Under these circumstances considerable pulmonary crippling may ensue.[11] Here, we wish

scoliosis, producing not only marked deformity but bellows inefficiency. Adequate physical therapy can do much to obviate this problem. Even if scoliosis is avoided, some deformity is inevitable The elevation of the rib cage is diminished, and ventilation on the operated side is less. In such cases, the remaining respiration depends almost entirely on diaphragmatic action Again, the importance of avoiding phrenic crush must be emphasized.

Resection

Excisional surgery is more appealing than thoracoplasty on a priori grounds, since it is preferable to remove a focus of infection. However, complications are considerably more likely with excision In spite of these hazards, resection is coming into wide use, as the major surgical approach to chronic localized pulmonary tuberculosis

Space take-up is unnecessary in segmental resection, in middle lobe resection (since the middle lobe is not very large) or after an irreversible emphysema has been proved to exist. (The latter may be demonstrated by study of the effects of pneumoperitoneum in a patient with, for example, a long-standing contracted lobe.) Where the upper or lower lobe or the whole lung is involved, the problem of space take-up must be considered. Lobectomy in children does not, as a rule, require space take-up; but even in children, it may be desirable to do a phrenic evulsion at the time of pneumonectomy. Case II (Figs. 4–7) demonstrates the

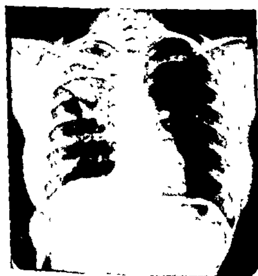


Fig 4 —(*Case II*) Preoperative x-ray of a 12 year old female with atelectasis of the major part of the right upper lobe



Fig 6 —(*Case II, continued*) Postoperative x-ray following right upper lobe resection Pneumoperitoneum has been instituted for space take-up in this 12 year old girl

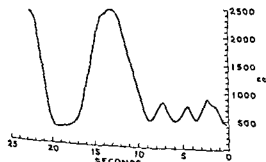


Fig 5—(*Case II, continued*) Preoperative spirogram showing a minor loss of vital capacity.

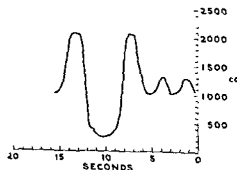


Fig. 7.—(*Case II, concluded*) Postoperative spirogram reveals marked improvement of both inspiratory and expiratory velocity

physiologic effects of collapse and excisional surgery, see Chapter 45.

Phrenic Nerve Interruption

Phrenic crush no longer has the valued reputation that it once held as a technic of collapse therapy. This is because the recovery of the diaphragm is often incomplete, and degeneration of the diaphragm with thinning and weakness of the musculature may persist after regeneration of the phrenic nerve. This may lead to atelectasis of the lower lobe, interference with bronchial drainage and disturbed pulmonary function. The effect of phrenic paralysis is, of course, to produce a paradoxical diaphragm, and ventilation in one lung may be considerably reduced. When surgery, particularly thoracoplasty, is planned for a later date on the side of a phrenic crush, a total inadequacy of ventilation on that side may result. For these reasons, phrenic paralysis is largely reserved for the postpneumonectomy case in which it is desirable for the diaphragm to rise considerably, obliterating as much of the hemithorax as possible.

Collapse Therapy Other Than Thoracoplasty

Collapse therapy with an intact chest wall has been the subject of intensive therapeutic research. In the prechemotherapeutic era, extrapleural pneumothorax was widely used. This has passed into relative disuse now because of its temporary nature and because of the difficulty of adequate control. It has been replaced in certain clinics by extrafascial *plombage* with plastic balls, sponges or bags. Physiologically, this type of surgical collapse therapy may be advantageous, since it retains the elevation of the rib cage on inspiration, so that normal tissue on the affected side is better used. This, of course, is even more true in extrapleural pneumothorax than plastic plombage. Plombage also has the clinical advantage of being highly selective. For these reasons, it is probably the surgical procedure of choice for the patient who is a poor physiologic risk for more extensive surgery. However, it has a much higher complication rate than thoracoplasty. Infection of the space is not uncommon, and even without infection, fluid collection may result in the collapse of a major part of the lung; and plastic balls have been known to perforate the facial layer and "wander" into various parts of the thorax. In the immediate postoperative period, pain may impede coughing, and the resultant collection of pulmonary secretions and debris may cause atelectasis and collapse elsewhere in the lungs. The pain may also cause further restriction of ventilation, giving rise to a tendency toward acidosis.

Collapse therapy does not deal with the problem of destroyed tissue, with its arteriovenous shunts, and so forth, and hence it is seldom entirely satisfactory. Late complications, such as the shifting of the plomb due to pressure necrosis, are fairly common. The procedure is still useful for the patient whose shortness of breath prohibits more extensive procedures, or for restricting disease activity in patients being prepared for resection and a tailoring thoracoplasty.

Thoracoplasty

At the present time, there are two kinds of thoracoplasty in general use, the primary therapeutic thoracoplasty designed to collapse, usually, a whole lobe, and the tailoring thoracoplasty presenting anterior rib parts, in which the intention is space take-up after excision. The physiologic disturbances are much the same for both types, and they are generally more severe than those accompanying plombage. These are primarily due to the loss of elevation of the rib cage, this is particularly marked in the case of the primary therapeutic thoracoplasty. In planning a therapeutic program for a patient, it must also be kept in mind that thoracoplasty may make reasonable posture, chest shape and ventilatory mechanics a problem for the patient. However, from a clinical point of view, immediate and late complications are less common than with plombage, although paradoxical respiration of the upper chest on the operated side may be a serious postoperative hazard to the patient whose ventilation is already restricted. Stabilization of the chest wall defect and intermittent positive pressure breathing will almost invariably solve this problem.

The late problem with a thoracoplasty is

scoliosis, producing not only marked deformity but bellows inefficiency. Adequate physical therapy can do much to obviate this problem. Even if scoliosis is avoided, some deformity is inevitable. The elevation of the rib cage is diminished, and ventilation on the operated side is less. In such cases, the remaining respiration depends almost entirely on diaphragmatic action. Again, the importance of avoiding phrenic crush must be emphasized.

Resection

Excisional surgery is more appealing than thoracoplasty on a priori grounds, since it is preferable to remove a focus of infection. However, complications are considerably more likely with excision. In spite of these hazards, resection is coming into wide use, as the major surgical approach to chronic localized pulmonary tuberculosis.

Space take-up is unnecessary in segmental resection, in middle lobe resection (since the middle lobe is not very large) or after an irreversible emphysema has been proved to exist. (The latter may be demonstrated by study of the effects of pneumoperitoneum in a patient with, for example, a long-standing contracted lobe.) Where the upper or lower lobe or the whole lung is involved, the problem of space take-up must be considered. Lobectomy in children does not, as a rule, require space take-up, but even in children, it may be desirable to do a phrenic evulsion at the time of pneumonectomy. Case II (Figs. 4–7) demonstrates the

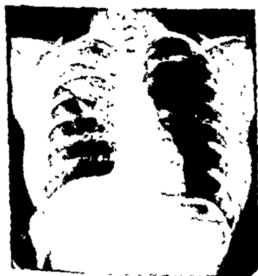


Fig. 4.—(*Case II*) Preoperative x ray of a 12 year old female with atelectasis of the major part of the right upper lobe.



Fig. 6.—(*Case II, continued*) Postoperative x-ray following right upper lobe resection. Pneumoperitoneum has been instituted for space take-up in this 12 year old girl.

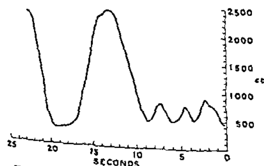


Fig. 5.—(*Case II, continued*) Preoperative spirogram showing a minor loss of vital capacity.

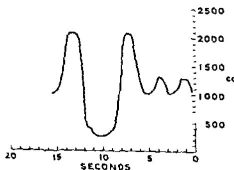


Fig. 7.—(*Case II, concluded*) Postoperative spirogram reveals marked improvement of both inspiratory and expiratory velocity.

marked improvement of airflow with little loss of vital capacity in a 12 year old girl with right upper atelectasis treated by right upper lobectomy and pneumoperitoneum

The immediate physiologic problems after resection are similar to those of any operation on the thorax pain with hypoventilation and impeded cough, favoring the retention of bronchial secretions. To these are added the loss of some functioning alveoli, when the resection has included normal lung tissue. In Case III (Figs 8–11) there is a real loss of vital capacity shown postoperatively. Any pre-existing emphysema presents its own problems. When a thoracoplasty is done at the time of lobar resection, paradoxical respiration may be quite marked Fluid is particularly likely to form in the pleural space, giving rise to pleural adhesions These may cause immobility of the diaphragm and chest wall, or tether the remaining lobe in the case of lobectomy. It is important to prevent the accumulation of excessive pleural fluid and also to avoid deflation of the remaining lobe after a lobectomy. Tailoring thoracoplasty should be considered in all cases in which a lobectomy is done, and

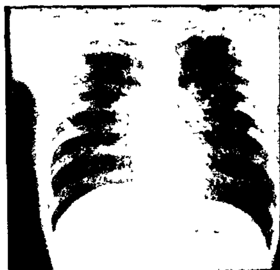


Fig 8—(*Case III*) Preoperative x-ray of a 42 year old male with pulmonary fibrosis involving most of the right upper lobe

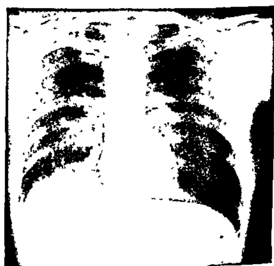


Fig 10—(*Case III, continued*) Postoperative x-ray of the patient following right upper lobe resection

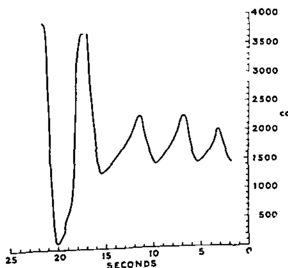


Fig. 9—(*Case III, continued*) Preoperative spirogram Relatively normal

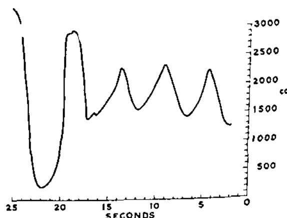


Fig 11—(*Case III, concluded*) Postoperative spirogram showing diminution of vital capacity with little if any lessening of expiratory velocity The loss appears in the inspiratory reserve.

in the case of pneumonectomy, a more extensive thoracoplasty is usually required, with or without a phrenic evulsion

Other Surgical Procedures

Cavernostomy, either with Monaldi drainage or with marsupialization of the cavity, has real value in patients with giant tension cavities who are unsuitable for other types of surgery. The physiologic impairments of this procedure are negligible, and when diminution of pulmonary reserve militates against more radical surgery, this operation may help control the patient's disease

Decortication has proved rather disappointing as an approach to chronic fibroid disease of the pleura. When pulmonary disease is extensive, the physiologic improvement of the patient's reserve may not be sufficient to justify the hazards of the procedure. Under these circumstances a space take-up operation may be preferable.

Decortication[16] is most useful in the treatment of a fibroid pleura resulting from a simple but persistent pleural effusion. It is especially suitable for younger patients, when lung changes are less likely to be irreversible. The chief complications are air leaks and pleurisy with some scarring. As with other procedures in which these complications occur, it is imperative to know something of the function of each lung separately before decortication is done, in order to estimate the hazard that either development would represent. This is even more urgent when bilateral disease exists. In the treatment of localized empyema, one's watchfulness should not be less, since serious loss of function of the lung on the operated side may still occur

Bronchoplasty is an operation relatively seldom performed in patients with tuberculosis, and our experience is as yet too limited to say more than that it is theoretically a useful procedure in patients with localized bronchostenosis but no bronchiectasis. Physiologically, it would be advantageous

Other procedures involving excision of cysts, "cotton-candy" lung, and so forth, are occasionally done in connection with tuberculosis and are of great physiologic interest. Operations designed to treat bronchopleural fistula with empyema by lateral thoracoplasty and drainage are relatively unsatisfactory; pulmonary function may be further impaired. These must be regarded as operations of necessity rather than of choice

Summary

The approach to therapy depends on an understanding of the pathophysiology involved. Since pulmonary tuberculosis is an important cause of cardiorespiratory disability, therapy aimed at such disability is of the greatest importance.

Mechanical factors include the best use of the muscles of respiration that can be obtained. This means that many patients may be considerably benefited by breathing exercises aimed at developing the greatest mechanical efficiency of ventilation. Particularly is this true when these patients suffer as well from pulmonary emphysema. With surgery, there may be considerable disturbance of the musculature of the thoracic cage together with actual changes in its configuration, as with thoracoplasty. The maintainance of the musculature and of the best posture to use it most effectively is a matter of extreme importance during the postoperative phase. The treatment of flail chest postoperatively does not need further amplification

The *airway* is a matter of considerable preoccupation among surgeons but sometimes escapes the physician's notice. Restricted ventilation may mean retained secretions. This is a common cause of infection with secondary organisms together with inflammatory and allergic responses. This will be further exacerbated by emphysema if present. Such measures as antibiotics, intermittent positive pressure breathing with bronchodilators, dilatation of stenotic major bronchi and similar measures are actually good examples of physiologic therapy in tuberculosis. All the aids which we have in the physiologic therapy of other respiratory cripples apply equally well to patients with pulmonary tuberculosis. Since these are discussed elsewhere in this book, we shall not give details here of their application

Localized intervention in areas thought to be

major causes of pulmonary dysfunction is a field of surgery still in its infancy, because physiologic methods of evaluation of specific areas are only now being developed. For this field to develop to its full it is necessary that we should all think of these possibilities.

The *prevention* of pulmonary disability by the early use of corticoids in therapy, by the prevention of compensatory emphysema, by the design of surgical procedures causing least disability and similar means is also in its infancy It is here that we are looking to the future.

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The Pneumoconioses

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Introduction

PNEUMOCONIOSIS, as the term is generally used *clinically*, applies to pulmonary conditions of industrial origin resulting from inhalation and retention in the lungs of mineral dust containing: silica, silicates, asbestos, coal, carbon, smoke, iron, alumina abrasives, chalk and others The dominant features of the condition with respect to disability are fibrosis or emphysema or both. Iron oxide may produce an abnormal roentgenologic pattern difficult to differentiate from silicosis, but without function impairment[24] Classification of industrial dust into harmful and inert categories is difficult, since some which are usually considered innocuous may under certain conditions produce definite pathologic changes after prolonged exposure Organic dusts of animal or vegetable origin are not included in discussion of the pneumoconioses, although they may excite allergic reactions, introduce infections, produce local irritation or toxic action Beryllium is not included, as the reaction produced in the lungs from inhalation of this very toxic substance is quite different from the fibrosis and emphysema characteristically noted in association with the other dusts listed above Pneumoconiosis is an important industrial problem because of the physical disability resulting and the employer liability under various Workmen's Compensation Laws.

Gardner[4] and others have demonstrated that silicosis is likely to develop *only* when significant concentrations of respirable size particles, those smaller than 5 microns, of free or uncombined silica are inhaled over a long period of time A natural barrier to dust inhalation is provided by the structure of the upper respiratory tract, in which the ciliated epithelium lining the bronchioles serves to catch and eliminate inhaled dust. Dust must be air borne to be inhaled and small enough in size to reach the alveoli. Particle sizes less than 5 microns are the most toxic. The diameter of an alveolus is *approximately* 250 *microns*, but very few particles of more than 10 microns in size ever reach the alveolar level to produce damage. The concept has been advanced that any dust when inhaled in sufficient quantities so as to plug part of the respiratory tract can mechanically produce disability. Coal dust has been advocated as a specific entity,[9] but it still remains to be proven that the silica, though it be small in amount, in coal dust is not the real offender. The presence of large amounts of carbon may delay the removal of the silica and permit longer action so that the quantity of silica required to produce damage when retained in the presence of coal dust is much smaller than otherwise. The experimental work of King[10] indicates that nonsiliceous dust, *including coal*, may potentiate the effect of a small amount of silica It also remains to be demonstrated that inhaled pure carbon per se can produce fibrosis and emphysema with disability The silicates vary greatly in pathogenicity. Some are apparently inert, others mildly pathogenic and some exert a retarding effect on the reaction of free silica Asbestos is the important silicate producing fibrosis The toxicologic properties of substances may be changed in manufacture, such as in refining diatomaceous earth, in which the heating and calcine process changes amorphous silicon dioxide to crystalline cristobalite, which is toxic and produces silicosis. Pneumoconiosis is most often seen in miners, quarriers, drillers, workers with powdered sand, in factory grinders, pottery workers, asbestos workers, diatomaceous earth workers, alumina abrasive workers (bauxite) and those making various commercial powders containing silica, especially scour-

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The remarks on symptoms, physical signs, diagnosis, pathology, physiology and treatment discussed in the following sections refer to *silicosis in general except as indicated*

Symptoms

The onset of pneumoconiosis is usually very slow, a period of years being required for symptoms to develop However, the diatomaceous earth type may be quite rapid developing symptoms in one or two years or even less[25] The disease may progress into an advanced stage with no symptoms except a tendency toward shortness of breath, which at first is noted on moderate exertion, but as the disease progresses the dyspnea becomes more and more severe Orthopnea is not a characteristic finding unless allergic asthma is present or there is an associated right heart failure Cough may be present, and if secretions are present, the quantity is usually the largest in the morning, commonly mucoid and gray in color in the absence of infection In the more advanced cases there is a gradual failure in health, loss of strength, loss of weight, poor appetite, digestive disturbances, pain in the chest (frequently described as feeling like a constricting band around the chest) and pleuritic adhesions. Hemoptysis is common and occasionally a spontaneous pneumothorax develops Tuberculosis presents the usual symptoms when associated wth pneumoconiosis, but progress of the disease is more rapid The tubercle *bacilli may be difficult* to demonstrate unless cavitation has occurred, as the fibrosis retards this activity Fever, night sweats, tachycardia *and weight loss characterize* tuberculosis complicating pneumoconiosis A latent tuberculosis may be obscured so that tests are *repeatedly negative for tuberculosis*, and in some instances even cavities may be present with negative bacteriology However, a *cavity may represent* an area of ischemic necrosis, especially in coal miners,[26] and not necessarily tuberculosis. The demonstration of tubercle bacilli associated with pneumoconiosis has a poor prognosis with a short life expectancy.[6] These individuals are difficult to treat as the various forms of collapse therapy are ineffective and the antibiotics are without value in many cases.

Dyspnea is due to the breathing impairment resulting from fibrosis and/or emphysema, a characteristic feature of the pneumoconiosis Fibrosis occurs in the absence of or with varying degrees of pulmonary emphysema In the absence of emphysema, the total lung capacity is reduced in fibrosis, but when associated with emphysema the total lung capacity may be decreased, increased or normal.[11] Dyspnea present with exertion is related to the increased work of breathing encountered when the pulmonary ventilation is increased in an attempt to get a sufficient amount of air in and out of the lungs to supply oxygen and remove carbon dioxide Chronic bronchitis is often present especially in coal miners, and this is frequently accompanied by large amounts of secretions, probably indicating the presence of a low-grade infection Wheezing and attacks simulating bronchial asthma occur in coal miners, although the history is not that of an allergic type of asthma[26] The wheezing is produced by the fibrous tissue proliferation which narrows the bronchioles, hence, slight relief results from the inhalation of a bronchodilator drug in this type of case Air distribution in the lung is impaired by the fibrosis as revealed by tests of intrapulmonary mixing, even *in* the absence of emphysema or demonstrable bronchospasm

Physical Signs

The physical signs of pneumonociosis may *be slight, sometimes even in the advanced* case[6] Chest expansion is frequently diminished, and there are usually signs of a general *bronchitis Many cases present a picture* of severe emphysema and bronchitis on physical examination Breath-holding is quite variable *and unreliable as a test* Occasionally, rhonchi and scattered fine or coarse rales are heard Marked differences may be noted between the physical examination and the changes revealed by the chest roentgenogram The onset of pneumoconiosis may be very slow, requiring 20 to 40 years or longer to develop disabling silicosis in coal miners,[14] while in other industries total disability may occur after a few years, such as exposure to diatomaceous earth[25] The disease may *persist and* even progress after exposure to the offending

dust has stopped. In some cases, the disability is very marked and dyspnea occurs with the slightest exertion along with progressive weakness The increased susceptibility to colds and other respiratory infections, especially various forms of pneumonia, is usually associated with emphysema and/or severe hypoxia

Diagnosis

The chest roentgenogram is most helpful in diagnosis, but cannot be relied on to evaluate the amount of disability present.[14] The diagnosis should not be made in the absence of an adequate work history or positive biopsy of the lung or scalene node. Some individuals may show roentgenologic changes after one year which take 8 to 10 years or longer to develop in another under similar work conditions There also appears to be an individual susceptibility factor related to mouth breathing, the presence of sinus infections, and associated conditions such as bronchitis, bronchiectasis, bronchopneumonia and particularly tuberculosis The characteristic shadows on the x-ray persist and practically never disappear A great deal of time and attention has been given to the classification of the x-ray appearance, *although this* seems somewhat unnecessary in view of the fact that the degree of pulmonary function impairment cannot be correlated with the changes noted on the chest films[14] The *following* x-ray classification has been fairly satisfactory as a clinical guide (1) *normal lung markings*; (2) *borderline*, increased peribronchial markings, (3) *first stage*, slight, fine mottling of the parenchyma and increased size and density of hilar lymph nodes; (4) *second stage*, the typical nodular round and oblong shadows of soft even density from 2 to 6 *mm* in diameter, (5) *third stage*, shadows more than 6 *mm* in diameter or conglomerate shadows and (6) the *linear type* without definite nodulation, but with variations in intensity of shadows A single film may have numerous combinations of the above present The pneumoconiosis may also be classified as (1) the *simple type*, either with linear or nodular markings (the pure nodular type is less common than the linear or mixed types) and (2) the complicated type, characterized by the presence of conglomerate masses or areas on the x-ray which usually indicate the presence of an infection Infection in pneumoconiosis as previously described is commonly associated with tuberculosis, although in many of the cases it may be very difficult to demonstrate the organism during life. The fibrosis produced may be extremely hard, firm and dense. The lobes of the lungs may be bound down so tightly, that in surgical explorations, a lobectomy cannot be performed, and once a resection is started, a pneumonectomy may be required The marked loss of lung elasticity is a very characteristic feature

The inhalation of asbestos, which is a silicate, and does not contain free silica produces a condition similar to silicosis in certain respects The character of the fibrosis on the chest roentgenogram tends to be linear and diffuse, especially at the lung bases in asbestosis, and it does not take on a nodular form as seen in silicosis However, the old idea that a nodular x-ray appearance is required to diagnose silicosis is no longer held

A complete history, physical examination and radiologic study provides important information for the clinical evaluation of impairment, however, such information frequently proves inadequate in an accurate determination of the extent of disability present, and in some cases even fails to indicate the nature of the respiratory difficulty In recent years, the discrepancy between roentgenologic studies and pulmonary function studies as an appraisal of disability produced by pneumoconiosis has become well recognized[5]

Pathology

In simple silicosis, the focal, discrete, hyaline, silicotic nodules and the whorled pattern of the collagenous fibers is described as the essential lesion The nodules are scattered, more or less uniformly, throughout the lung parenchyma, under the pleura and in the hilar nodes Phagocytosis is usually regarded a primary feature in removing particles in the alveoli. The phagocytes originate in the walls of the alveolar septa, and after ingestion the particles migrate to the alveolar duct, some are disposed of by ciliary action and others enter the lymphatics to evoke a foreign body response with fibrous tissue formation More re-

cently a new concept on the pathogenesis of silicosis[8] suggests that the silica particles penetrate into the lung interstitium without the aid of phagocytes. Silicotic nodules result from *proliferation of cells of the alveolar wall in* clusters that enlarge and become collagenized. The lymph nodes at the lung bases are usually fibrosed with many laminated whorls in the periphery. With progression, the miliary nodules become coalesced forming dense fibrous masses, with many adhesions, thickened pleura *and even tenting of the diaphragm. Bronchitis* is usually present, associated with the fibrosis. In asbestosis, the long fibers initiate the fibrous tissue response by a mechanical irritation. The identification of the "asbestos body" from lung biopsy sections makes the diagnosis in asbestosis.

Coal dust forms nodules which occur in small foci scattered throughout the lungs in the simple pneumoconiosis. Collections of coal dust accumulate around the smaller bronchioles[9] and accompany the blood vessels. The coal dust particles have apparently been engulfed by phagocytes in the alveoli and brought by the lymph channels to the place of deposition. Delicate reticulum fibrosis develops within the foci of dust, while in others collagen fibers occur. The collagen fibers, however, do not develop the characteristic appearance of classic fibrosis. There is an irregular and haphazard appearance of collagen fibers running in a mesh work throughout the dust foci. Around the coal nodules the air spaces are frequently dilated, sometimes grossly, with the characteristic appearance of focal emphysema as described by Gough.[7] Foci of coal nodules often increase in size until they impinge on each other and become coalescent. In addition, the organic matter in coal dust may have some unrecognized chemical property which stimulates and effects the production of fibrous tissue, although the siliceous matter in coal dust is probably the chief factor. Silica is found by *microincinerations* in sections of the lungs of coal workers and even those of coal trimmers (coal loaders on ships), and this suggests that the small amount of contained silica is the real fibrogenic agent which *causes production of* the reticulum of collagen in the coal nodule.

The focal emphysema starts around bronchioles.[9] The infective variety of the coal workers' pneumoconiosis is due to the combined reaction of the dust and infection with progression of the coal foci to massive fibrosis. The masses occur unilaterally or bilaterally, but most frequently in the upper and posterior parts of the lung. The chest roentgenogram does not always show the characteristic nodules of uncomplicated silicosis. Actually, diffuse symmetric nodulation is seen infrequently in coal *miners, being more often a linear pattern or* a mixture of linear, nodular or conglomerate types of fibrosis. Ample evidence has been produced to show that pulmonary nodulation is not necessary for the roentgenographic or post-mortem identification of coal miners' pneumoconiosis.

Physiologic Disturbance

The large pulmonary reserve in man often obscures and delays clinical and roentgenologic detection of early pathologic changes of fibrosis and emphysema before clinical symptoms are prominent. The major physiologic changes in the pneumoconioses consist of impairment in alveolar aeration on the ventilatory side, of hypoxia and hypercapnia from disturbance in the transport of oxygen and carbon dioxide in the lung and a decreased pulmonary blood flow during exercise from lack of expansibility of the pulmonary vascular bed.[14] In the large majority of cases of pneumoconiosis with dyspnea, *the disability is due* to fibrosis and emphysema. The data for the discussion on physiologic disturbances have been obtained during the past 12 years from extensive pulmonary function studies on over 600 anthracite coal miners, 100 bituminous coal miners, 100 diatomaceous earth workers and smaller numbers of hard rock miners, pottery and asbestos workers.

The pulmonary function was evaluated *from* the following measurements as described below. The lung volume measurements consisted of spirograms on the 13.5 L. respirometer before and after bronchodilator drugs such as Vaponefrin and Isuprel. The measurements *from the spirogram included total* vital capacity, forced expiratory capacity for three sec-

onds ($FEC_{3.0}$) and the maximal breathing capacity. The shape of the spirogram tracing was also of significance The residual volume was measured and checked by the oxygen open circuit,[15] and for the past five years both the oxygen open and the helium closed circuit methods.[17] The alveolar nitrogen was obtained on oxygen breathing with the residual volume open circuit method, and for the past five years after the end tidal nitrogen was reduced to one per cent as monitored by the nitrogen meter. The oxygen content, oxygen capacity, CO_2 content and pH were obtained on resting and exercise samples of the arterial blood, employing the manometric Van Slyke apparatus. The arterial blood oxygen saturation was determined both from oxygen content and capacity measurements and by employing the Waters double-scale cuvette oximeter for blood. The oxygen capacity was checked both by the flask and Van Slyke methods. Arterial blood samples were obtained at rest and with exercise on air, various levels of low and high oxygen breathing and with intermittent positive pressure breathing on compressed air The subject was allowed to breath the low or high oxygen for 8 to 10 minutes before the exercise was started The pulmonary ventilation measurements (including the minute volume of air breathed, the oxygen uptake, the carbon dioxide output and the per cent of oxygen extracted from the inspired air breathed) were obtained from gas analysis, using the Scholander apparatus, of the expired air collected in a Tissot gasometer The effective tidal air was calculated from the expired Pco_2 and the arterial Pco_2,[21] the latter measurement by the direct bubble tension technic[22]

Pulmonary emphysema as the term that is used clinically, refers to an overinflation or distention of the lung (localized or diffuse), characterized by a relative increase in the amount of air which cannot be blown out with forced expiration The residual volume per cent of total lung capacity has been found to represent a reliable consistent reference measurement, and in general the average ratio does not change significantly from the supine or standing position or even when walking on a treadmill The functional residual capacity (residual plus expiratory reserve) does vary significantly from the supine to standing position because the change in the level of the diaphragm increases the expiratory reserve Mild exercise frequently increases the functional residual capacity

The predicted ratio of residual volume to total lung capacity as used in this study for the various age groups was as follows: under 35 years of age 20 per cent, from 35 to 60 years of age 25 per cent and above 60 years of age 30 per cent More recent studies in this laboratory correlating the nitrogen wash-out curves with a nitrogen meter and the ratio of residual per cent of total lung capacity, indicate the following In most cases of emphysema of a moderate degree the residual ratio is between 35 to 50 per cent of total lung capacity, of a severe degree between 50 and 65 per cent and for a very severe degree above 65 per cent. The residual per cent of total lung capacity may be elevated in some cases of severe restrictive conditions of the chest in which emphysema is not a significant factor, because the vital capacity is so low and the residual volume is not decreased proportionately. This type of case is easily recognized by the normal values for intrapulmonary mixing. The spirogram reveals no prolonged expiration, the total lung capacity is decreased, and in some cases the maximal breathing capacity is much better than the vital capacity with respect to predicted values[19, 28] The severity of the emphysema is best evaluated from the absolute volume of the residual volume, the ratio of residual to total lung capacity, changes in total lung capacity with respect to the predicted value, tests on impairment in air distribution in the lung, the total vital capacity with respect to the predicted and the shape of the forced expiratory spirogram No single test is adequate to evaluate emphysema The lung volume tests as described provide information with respect to the ability of the individual to move air down to the alveolar level where the oxygen can be taken in and the carbon dioxide blown off The ventilatory abnormalities or the inability to adequately aerate the alveoli represent a major difficulty in pneumoconiosis[11]

To evaluate the efficiency of the chest and lungs as a bellows to provide alveolar ventila-

tion, a numeric ventilation factor (VF)[15] has been devised from the average of three measurements, all expressed as per cent of the normal predicted, namely: the three second forced expiratory capacity (expressed as per cent of the normal predicted vital capacity), the maximal breathing capacity and the residual air as per cent of total lung capacity. This ventilation factor presents a single quantitative measure of the individual's ability to use the chest and lungs as a bellows for aerating the alveoli and is well correlated with the arterial P_{CO_2} as determined by direct tension measurements (Fig. 1). If the VF is normal (100 per cent or more), then the alveoli are adequately aerated, but if decreased to as low as 25 per cent, dyspnea is usually present even at rest.[15]

The pulmonary function data on 500 coal miners with pulmonary complaints (both anthracite and bituminous) are presented in Table 1 and correlated with the VF. The VF was used to correlate the data on pulmonary

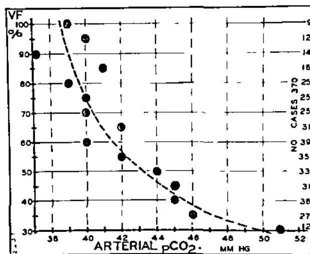


Fig. 1—Correlation of the arterial P_{CO_2} in mm Hg with the ventilation factor (VF) in 370 cases of coal miners pneumoconiosis. The arterial P_{CO_2} was determined in all cases by the direct bubble technique. The cases were divided into 15 groups based on the VF per cent with step decreases of 5 per cent from 100 to 30 (for example 33 cases are listed with a VF of 50 per cent, which includes all cases with a range from 47.51 to 52.5 per cent). The number of cases in each of the 15 groups is shown in the column on the right. The data indicate that the arterial P_{CO_2} level is a function of alveolar aeration, and that there is a correlation with the ability to use the chest and lungs as a bellows as measured by the VF to provide alveolar aeration and blow off CO_2.

function in the 500 coal miners, since it is a better single measurement (average of three separate tests) than the residual per cent of total lung capacity for correlating alveolar ventilation. The 15 groups given in Table 1 were separated on the basis of the VF. About 20 per cent of the cases presented in Table 1 were bituminous coal miners, but the function measurements were indistinguishable from the anthracite coal miners. The measurements given in Table 1 are representative of the pneumoconiosis as a whole, and illustrate the complete range from normal function with progressive changes in function impairment to total disability.

Emphysema and fibrosis in various degrees occur in pneumoconiosis. The total vital capacity may be normal, increased or reduced. The forced expiratory capacity for three seconds ($FEC_{3.0}$) is decreased in the presence of emphysema, usually of the obstructive type, significantly below the total vital capacity. The maximal breathing capacity is usually decreased farther below the predicted normal than is the $FEC_{3.0}$ (Table 1). When fibrosis is the dominant aspect without significant emphysema, as seen in some cases of asbestosis, the maximal breathing capacity may be increased considerably above the $FEC_{3.0}$ or the VC with respect to predicted normal, and the exhalation time is normal. The residual air is increased in emphysema in varying degrees and uneven air distribution is present. Some alveoli are normally ventilated, others poorly ventilated and some are not ventilated at all, as the air cannot pass the obstruction of the bronchi produced by mucus and secretions, bronchospasm, infection, edema or fibrosis. The nonventilated alveoli may have blood perfusion in the capillaries but no gas exchange. Bronchospasm is of common occurrence and can usually be demonstrated by taking the maximal breathing capacity before and after a bronchodilator treatment with Vaponefrin or Isuprel. After treatment with bronchodilator drugs, some reduction in the residual air may be present and some increase in vital capacity observed, but the normal state is not restored and the change in the residual air per cent of total lung capacity is

usually of small magnitude A marked degree of bronchospasm may be observed in some cases without an increased residual volume

The blood gas exchange has been evaluated from measurements on arterial blood and expired air both at rest and during mild exercise (one minute step-up on an 8 inch stool and treadmill walking flat at two miles per hour [TABLE 2]) The step-up exercise test for one minute, although an unsteady state, provides comparable changes in the blood gas exchange as the treadmill (TABLE 2). Decreases in the arterial blood oxygen saturation represent a common finding in pneumoconiosis[12] The resting saturation is frequently in the low 90 per cent range at sea level With very mild exercise, the saturation may decrease 5 to 10 per cent or more in some cases, increase a few per cent in others or show no change A comparison of the exercise arterial blood saturation and the resting measurement is most important in disability evaluation If the arterial saturation drops 5 per cent or more with exercise, a severe degree of function impairment is indicated, whereas if the saturation increases above the resting value with exercise the severity of the function impairment is more often only slight or moderate in degree. If hypoxia is present at rest or with exercise on air breathing, simple tests are used to identify the cause The changes in the arterial blood oxygen saturation occurring during (1) intermittent positive presure breathing with compressed air only and (2) graded levels of high oxygen breathing (30 to 40 per cent oxygen and 100 per cent oxygen), both with rest and exercise, provide most simply the information as to the factors producing the hypoxia.[18] In some cases, low levels of oxygen breathing were used [13]

The use of intermittent positive pressure breathing (IPPB) on compressed air only (no bronchodilators) has been used as a diagnostic test to demonstrate the presence of poorly ventilated alveoli[13] The pressure breathing on compressed air does not elevate the mean inspired Po_2 in a sufficient degree to be a factor in overcoming an alveolar-capillary membrane block if present in a significant degree at the pulmonary membrane Studies with high and low levels of oxygen breathing (11 5 per cent and 27 8 per cent) when compared with the IPPB on compressed air only,[13] indicate that changes in the arterial Po_2 could not be correlated with the mean alveolar Po_2 on IPPB (FIG 2) The only way one can explain the improvement noted with IPPB on the compressed air is the presence of a more uniform alveolar aeration due to better inflation of those alveoli that have an impaired air circulation on ambient breathing In most cases, the IPPB partially corrects the impairment in the uniformity of alveolar aeration resulting from the fibrosis and the attendant loss of elasticity also accentuated by bronchospasm and produces a significant rise in the arterial blood oxygen saturation In some cases the deeper breathing with exercise produces a more uniform alveolar aeration, and the arterial blood oxygen saturation increases by a mechanism similar to the increased saturation produced by IPPB on compressed air only.

Rest and exercise represent two different hemodynamic situations in the same individual, and the blood flow through the lung with an increased cardiac output during exercise may be distributed differently with respect to perfusion of the better ventilated alveoli as compared to rest. More capillaries tend to open up with exercise in areas in which ventilation perfusion abnormalities are most extensive If the saturation drops markedly with exercise, this may be due to a diffusion difficulty (alveolar-capillary membrane block), to shunting of blood through nonventilated areas either in the lung or in the heart (right-to-left), or to a gross inability to ventilate the lung (individuals unable to breath enough air in and out to supply the necessary increased oxygen uptake) If the lowering of the arterial blood oxygen saturation with exercise results primarily from an alveolar-capillary membrane block, then breathing a high oxygen breathing mixture (30 to 40 per cent) with an increased inspired Po_2 (over 60 to 130 mm Hg above air breathing at sea level) should elevate the arterial blood oxygen saturation to the normal level of 97 per cent or more, as this is an adequate pressure increase for oxygen to overcome a membrane block, if this be the significant factor producing the hypoxia A 30 to 40 per

TABLE 1 —*Pulmonary Function Measurements on 500 Coal Miners* Correlated with the Ventilation Factor (VF)*

Ventilation Factor %	100	95	90	85	80	75	70	65	60	55	50	45	40	35	30
Number Cases	15	14	18	21	34	32	31	37	46	43	46	46	52	42	23
Age in Years	*45*	*46*	*49*	*52*	*52*	*51*	*55*	*54*	*55*	*56*	*54*	*56*	*56*	*53*	*55*
Inside Mine Exposure, Years	25	22	28	29	31	29	33	33	32	33	31	35	31	30	32
BSA M^2	1 86	1 82	1 85	1 87	1 86	1 82	1 90	1 84	1 76	1.79	1 79	1 75	1.74	1 71	1.74
Supine inspiratory reserve, ml	3248	3013	2748	2827	2578	2475	2384	2085	1936	1810	1640	1380	1225	1022	918
Supine expiratory reserve, ml	960	1144	1008	862	898	991	830	835	934	904	868	892	903	815	833
Vital capacity, ml															
rest supine, observed	4482	4487	3999	3924	3786	3821	3536	3210	3172	2941	2763	2497	2404	2095	1898
% Predicted	106 4	104 1	96 3	92 4	91 1	91 6	84 6	80 0	78 0	74 4	68 0	61 9	59 2	51.9	47.1
Three second forced expiratory capacity, cc															
standing, observed	4340	4345	3592	3690	3460	3140	3140	2630	2464	2174	2080	1840	1652	1414	1225
% predicted	103 2	100 9	86 5	87 0	82 5	73 7	73 4	65 0	60 7	55 0	49 9	45 5	39 8	35 1	30 4
Maximal breathing capacity, L /min															
observed	*144*	*134*	*122*	*108*	*105*	*96*	*84*	*79*	*63*	*57*	*50*	*44*	*35*	*30*	*22*
% predicted	103	98 8	90 7	82 0	79 6	72 9	62 9	61 5	51 2	45 8	39 5	37 0	29 3	24 9	18 7
Residual volume, ml	1356	1955	1541	1662	1784	1899	1774	1917	1955	2060	2114	2278	2500	2715	3399
Residual % total lung capacity	22 8	29 8	27 5	29 7	30 2	33 1	33 8	36 7	37 8	40 8	43 0	47 2	50 6	56 8	63 2
Alveolar nitrogen, %	1 43	2 06	1 40	1 94	1 68	1 95	1 95	2 40	2 57	2 95	2 77	3 75	3 87	4.59	5.46
Arterial O_2 content, volumes %															
rest	19 1	19 1	19 3	18 8	18 6	18 4	18 7	18 5	18 2	18 2	18 2	18 0	17 7	18 0	18.1
step-up exercise	20 1	20 4	20 4	20 1	19 8	19 5	20 1	19 4	19 0	18 8	18 8	18 8	18 1	17 8	17.8
Arterial oxygen saturation %															
rest	94 4	94 6	94 8	93 2	93 6	93 2	93 2	93 0	93 4	91 6	92 1	91 4	91 9	90 8	*90 2*
step-up exercise	94 8	95 0	95 1	94 1	94 2	93 5	94 3	93 0	92 1	90 5	90 5	90 7	88 9	84 5	83.4
Arterial CO_2 content, volumes %															
rest	45 8	47 1	45 8	46 3	46 0	46 6	47 1	47 1	47 6	48 0	49 5	49 8	49 9	51 8	54 1
step-up exercise	43 9	44 7	43 5	43 1	44 1	44 1	45 7	44 6	45 5	45 8	47 2	47 7	47 9	51 4	53.0
Hemoglobin, Gm	*15 2*	*15 2*	*15 1*	*14 5*	*14 3*	*14 2*	*14 5*	*14 3*	*14 1*	*14 4*	*14 2*	*14 2*	*13 9*	*14 3*	*14 5*
Hematocrit %															
rest	42 3	42 5	41 3	44 6	41 3	42 0	42 2	42 3	41 5	42 7	42 7	43 8	41.6	44 4	42 9
step-up exercise	44 1	44 5	42 6	46 5	44 0	44 3	45 7	45 1	44 0	45 3	44 5	46 0	44 3	46 6	45 8
Ether, circulation time, seconds	6 2	6 2	6 3	7 9	7 8	7 7	9 2	7 6	7 2	7 6	7 5	7 4	8 1	7 9	7 9
Decholin, circulation time, seconds	15 1	14 7	15 9	15 6	16 1	16 1	18 6	15 9	15 5	16 1	15 5	16 4	15 9	16 4	16 0
Arterial pH															
rest	7 47	7 45	7 46	7 45	7 46	7 45	7 45	7 44	7 45	7 43	7 44	7 43	7.44	7 43	7 43
step-up exercise	7 42	7 43	7 42	7 44	7 43	7 43	7 43	7 42	7 43	7 40	7 44	7 43	7.40	7 39	7.40
Pulse rate/min															
rest	68	74	70	78	68	69	71	70	73	76	75	75	79	81	80
step-up exercise	93	113	102	109	101	107	97	110	104	106	106	106	111	112	116
Respiration rate/min															
rest	20	17	19	20	20	18	19	20	20	21	20	20	19	21	21
step-up exercise	26	25	25	26	27	26	27	26	26	31	28	28	30	31	30
Minute Ventilation L /M^2/BSA.															
rest	4 4	3 8	4 2	4 3	4 5	4 3	4 1	4.1	4 4	4 4	4 5	4 4	4 4	4.6	4.3
step-up exercise	11.4	12 2	11 2	12.7	13.2	12 3	13 3	12 2	11 7	12 2	11 4	10 9	10 5	9 7	8 5

TABLE 1.—*Continued*

Tidal volume, ml															
rest supine	421	421	418	416	438	462	428	433	414	384	424	409	417	391	376
step-up exercise	805	898	914	930	913	895	898	864	802	707	739	693	612	548	512
Oxygen removed from inspired air, %															
rest	3 36	3.59	3 47	3 36	3 22	3.36	3 43	3 41	3 28	3 24	3 25	3 27	3 28	3 22	3 28
step up exercise	4 79	4 45	4 72	4 17	4 13	4 29	4 19	4 23	4 01	4 14	3 95	4 17	3 84	3.88	4 05
CO_2 output, ml /min / M^2/BSA															
rest	111	110	112	114	117	116	111	110	114	114	115	115	113	117	111
step up exercise	374	397	361	319	404	361	399	370	345	348	322	310	284	278	250
O_2 uptake, ml /min / M^2/BSA															
rest	132	138	140	141	141	141	138	137	139	141	140	139	138	144	137
step up exercise	546	526	518	515	523	505	533	501	461	487	442	441	379	368	341
Dyspnea, step-up exercise, sec	85	90	99	126	112	108	136	124	119	150	135	141	163	180	135

* Anthracite and bituminous miners from Pennsylvania and West Virginia.

cent oxygen breathing gas will not usually obscure the small shunt with exercise, but breathing 100 per cent oxygen does frequently obscure it, especially at rest,[18, 19] because the oxygen dissolved in the plasma is very markedly increased and the Po_2 very high When the saturation is 99 to 100 per cent on 100 per cent oxygen breathing the presence of large right-to-left shunts is ruled out.

In coal miners' and diatomaceous earth workers' pneumoconiosis, the reduced saturation at rest occurs because many alveoli are poorly ventilated on ambient breathing, some alveoli are poorly aerated yet perfused with blood either normally or with a decreased amount, other alveoli are perfused but not aerated (this is actually the small shunt at the alveolar level), and some alveoli are ventilated but not perfused with blood (FIG. 3)[13, 18] A high oxygen breathing gas (30 to 40 per cent) does not correct the unsaturation with exercise in pneumoconiosis because of alveoli perfused but nonaerated, but it does correct for the inequalities of air distribution from poorly ventilated alveoli. The distribution factor is the term frequently applied to the aspect most commonly involved, producing interference with the alveolar-arterial gas exchange (oxygen and carbon dioxide transfer in the lung) in pneumoconiosis. (FIG 3) Distribution refers to unequal alveolar aeration and perfusion The aeration factor concerns alveolar ventilation At sea level the alveolar mean Po_2 is normally about 100 mm. Hg and blood perfusing alveoli will take up oxygen to a Po_2 level of about 95 mm Hg (normally saturated 96 per cent). Alveolar aeration is impaired by loss of elasticity, fibrosis, obstruction from mucous plugs, secretions, partial atelectasis or depressed respiratory movements, as all of these restrict the free movement of air in and out of the alveoli Impaired alveolar aeration results in a lowering of the partial pressure of oxygen in the alveoli involved. Blood perfusing poorly aerated alveoli is incompletely saturated but flows to the left side of the heart to mix with the normally saturated blood. The perfusion aspect of the distribution factor also includes those alveoli

TABLE 2—*Comparison of Step-Up Exercise and Treadmill Exercise in 100 Cases of Coal Miners Pneumonoctosis*

Arterial O_2 Saturation		O_2 Uptake	O_2 Extracted from Inspired Air	Ventilation Volume
	%	ml / min / M^2/ BSA	%	L /min / M^2/BSA
Rest	92 7	144	3 32	4 39
Step-up exercise 1 min	91 0	476	4 04	11 97
Treadmill exercise 2 miles per hour, flat after 10 min	92.9	448	3 89	11 96

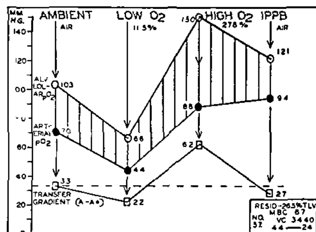


FIG 2—Diagram showing changes in alveolar and arterial Po_2 with ambient air breathing compared with low and high oxygen levels and intermittent positive pressure breathing (IPPB) on compressed air in a pneumoconiosis patient with fibrosis, but no significant degree of pulmonary emphysema The mean A-A or transfer (alveolar-arterial Po_2 difference) gradient was 33 mm Hg on ambient air breathing The A-A gradient decreased on low oxygen (11.5 per cent O_2), increased on high oxygen (27.8 per cent O_2), and decreased with IPPB on air Note that the mean arterial Po_2 was increased with IPPB more than on the high oxygen breathing (94 as compared to 88 mm Hg), although the mean alveolar Po_2 was considerably higher on the 27.8 per cent O_2 breathing (150 as compared to 121 on IPPB) The IPPB on compressed air produces a more uniform alveolar aeration of those alveoli poorly ventilated by ambient breathing (see FIG 3), but still perfused with blood and thus increases the arterial Po_2 more in proportion than occurs with the elevated alveolar Po_2 of ambient breathing on high oxygen The mean alveolar Po_2 was calculated from direct tension measurements of arterial Pco_2 and Po_2 and the RQ of the simultaneously collected expired air There was no evidence of an alveolar-capillary membrane block from these data

with complete blockage of aeration, but those in which the blood supply is maintained Such a situation amounts to little shunts, there being no gas exchange in the blocked alveoli Other alveoli may be ventilated but not perfused, because the capillary blood supply is obliterated by fibrosis, thrombosis or vasoconstriction The aerated but nonperfused alveoli are physiologic dead space and decrease the efficiency of lung ventilation The distribution factor has been found to be independent of the degree of pulmonary emphysema in pneumoconiosis [13]

The presence of an alveolar-capillary membrane block has not been found to be a significant factor in the pneumoconiosis Even in interstitial pulmonary fibrosis, sarcoidosis and other restrictive conditions of the lungs, without significant emphysema, the hypoxia principally results from the perfusion of blood through nonventilated areas and not an alveolar-capillary membrane block [10] A study of the oxygen transfer in *coal miners' pneumoconiosis* reveals an inability to maintain a normal alveolar Po_2, in the presence of severe emphysema as calculated from direct measurements of arterial Po_2, arterial Pco_2, the tidal volume and the RQ of the expired air.[12] The transfer of oxygen from the alveoli to the arterial blood is impaired in various degrees by the presence of poorly ventilated alveoli and by the *shunting of blood through non*ventilated areas, especially during exercise. In pneumoconiosis in general, oxygen gets across the pulmonary membrane in proportion to the partial pressure of the oxygen in the individual alveoli No evidence of a significant alveolar-capillary membrane block difficulty has been found in hard or soft coal miners' pneumoconiosis, in diatomite pneumoconiosis or in silicosis due to hard rock mining or pottery working In our experience in asbestosis, the primary difficulty has been the presence of poorly ventilated alveoli and the perfusion of blood through nonventilated areas of the lungs or very poorly ventilated areas, especially with exercise Even on a high oxygen breathing mixture (30 per cent O_2), in asbestosis with exercise the arterial saturation was still low (TABLE 3) In 4 cases, the decrease in saturation on 30 per cent O_2 with exercise as compared to rest indicates factors other than the level of the alveolar Po_2 as primarily involved (TABLE 3). The drop in saturation with exercise indicates the perfusion of some blood through nonventilated areas of the lungs in asbestosis.

A low diffusing capacity measurement (as the carbon monoxide steady state method[3]) is *not necessarily related to an alveolar-capillary* membrane block, but rather to a number of other factors, the reduced surface area for gas exchange probably being the major factor in

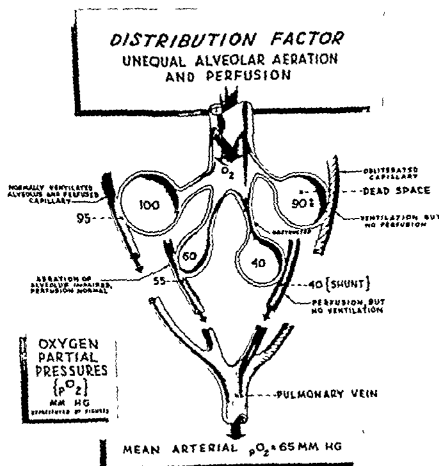


FIG 3—A schematic diagram indicating the disturbed relationship between alveolar aeration and perfusion in pneumoconiosis as produced by fibrosis, emphysema, secretions, bronchospasm, atelectasis or depression of the respiration and ventilation Four alveoli and capillaries (one normal, three abnormal) are shown in the above diagram The alveolus on the left has a normal ventilation-perfusion relationship The alveolus, second from the left, has impaired aeration because of a narrowing of the bronchiole and a low alveolar P_{O_2} (60 mm Hg), and the capillary blood leaves with a P_{O_2} of 55 mm Hg (marked degree of unsaturation of the hemoglobin) However, the oxygen gets across to the blood in proportion to the partial pressure in the alveolus (60 to 55) The alveolus third from the left has a completely obstructed bronchiole with no alveolar ventilation, and the blood perfusing the alveolus gives off no carbon dioxide and receives no oxygen (no gas exchange and a functional small right-to-left shunt) The alveolus on the right has no blood supply (ventilation but no perfusion), and this increases the functional dead space and decreases lung ventilation efficiency Intermittent positive pressure breathing (IPPB) increases the alveolar P_{O_2} in those alveoli which have impaired aeration with a resulting increase in the saturation of the blood perfused The IPPB has no effect on the oxygen transfer in alveoli which are perfused but nonaerated or alveoli which are ventilated but not perfused Elevating the inspired oxygen tension (P_{O_2}) corrects for the unequal alveolar aeration, increases the arterial P_{O_2} and the hemoglobin saturation to the normal range and may compensate for small shunts at the alveolar level if the extent is not too great However, if the extent of the shunting is great enough, even 100 per cent oxygen does not completely saturate the hemoglobin in the arterial blood

most instances The diffusing capacity measurements for carbon monoxide are markedly decreased in most cases of severe emphysema and/or fibrosis, and in our experience there is no evidence of an alveolar-capillary membrane block, but the alveolar surface area for gas exchange is markedly decreased.

The carbon dioxide content of the arterial

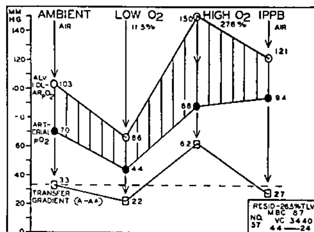


Fig 2—Diagram showing changes in alveolar and arterial Po_2 with ambient air breathing compared with low and high oxygen levels and intermittent positive pressure breathing (IPPB) on compressed air in a pneumoconiosis patient with fibrosis, but no significant degree of pulmonary emphysema The mean A-A or transfer (alveolar-arterial Po_2 difference) gradient was 33 mm Hg on ambient air breathing The A-A gradient decreased on low oxygen (11.5 per cent O_2), increased on high oxygen (27.8 per cent O_2), and decreased with IPPB on air Note that the mean arterial Po_2 was increased with IPPB more than on the high oxygen breathing (94 as compared to 88 mm Hg), although the mean alveolar Po_2 was considerably higher on the 27 8 per cent O_2 breathing (150 as compared to 121 on IPPB) The IPPB on compressed air produces a more uniform alveolar aeration of those alveoli poorly ventilated by ambient breathing (see Fig 3), but still perfused with blood and thus increases the arterial Po_2 more in proportion than occurs with the elevated alveolar Po_2 of ambient breathing on high oxygen The mean alveolar Po_2 was calculated from direct tension measurements of arterial Pco_2 and Po_2 and the RQ of the simultaneously collected expired air There was no evidence of an alveolar-capillary membrane block from these data

with complete blockage of aeration, but those in which the blood supply is maintained Such a situation amounts to little shunts, there being no gas exchange in the blocked alveoli. Other alveoli may be ventilated but not perfused, because the capillary blood supply is obliterated by fibrosis, thrombosis or vasoconstriction The aerated but nonperfused alveoli are physiologic dead space and decrease the efficiency of lung ventilation The distribution factor has been found to be independent of the degree of pulmonary emphysema in pneumoconiosis [13]

The presence of an alveolar-capillary membrane block has not been found to be a significant factor in the pneumoconiosis Even in interstitial pulmonary fibrosis, sarcoidosis and other restrictive conditions of the lungs, without significant emphysema, the hypoxia principally results from the perfusion of blood through nonventilated areas and not an alveolar-capillary membrane block [10] A study of the oxygen transfer in coal miners' pneumoconiosis reveals an inability to maintain a normal alveolar Po_2, in the presence of severe emphysema as calculated from direct measurements of arterial Po_2, arterial Pco_2, the tidal volume and the RQ of the expired air [12] The transfer of oxygen from the alveoli to the arterial blood is impaired in various degrees by the presence of poorly ventilated alveoli and by the shunting of blood through nonventilated areas, especially during exercise In pneumoconiosis in general, oxygen gets across the pulmonary membrane in proportion to the partial pressure of the oxygen in the individual alveoli No evidence of a significant alveolar-capillary membrane block difficulty has been found in hard or soft coal miners' pneumoconiosis, in diatomite pneumoconiosis or in silicosis due to hard rock mining or pottery working In our experience in asbestosis, the primary difficulty has been the presence of poorly ventilated alveoli and the perfusion of blood through nonventilated areas of the lungs or very poorly ventilated areas, especially with exercise Even on a high oxygen breathing mixture (30 per cent O_2), in asbestosis with exercise the arterial saturation was still low (Table 3) In 4 cases, the decrease in saturation on 30 per cent O_2 with exercise as compared to rest indicates factors other than the level of the alveolar Po_2 as primarily involved (Table 3) The drop in saturation with exercise indicates the perfusion of some blood through nonventilated areas of the lungs in asbestosis

A low diffusing capacity measurement (as the carbon monoxide steady state method[3]) is not necessarily related to an alveolar-capillary membrane block, but rather to a number of other factors, the reduced surface area for gas exchange probably being the major factor in

gen uptake reduced, a decreased pulmonary blood flow is indicated[20] Many pneumoconiosis patients with severe emphysema are unable to increase the pulmonary blood flow in extent corresponding to the degree of exercise given because of changes in pulmonary vascular resistance. The inability to increase the pulmonary blood flow with exercise because of increased pulmonary vascular resistance and the lack of expansibility of the pulmonary vascular bed, constitute very characteristic findings of the emphysema and fibrosis in pneumoconiosis[14] Cor pulmonale is present in most of the severe cases of fibrosis and emphysema. Right heart failure is the common cause of death Wells[27] observed by post-mortem studies that almost half of 136 miners with massive fibrosis died of cor pulmonale

Dyspnea is the most common complaint in pneumoconiosis resulting from the fibrosis and/or emphysema Dyspnea commonly results from an alteration in breathing resistance, such as elasticity changes and bronchial obstruction The impairment in elasticity in emphysema results in loss of lung tension and produces the ball-valve effect especially during a forced exhalation[2] Bronchial obstruction may be either permanently fixed or capable of being reversed in various degrees by bronchodilator drugs applied as aerosols The reversible type is referred to as bronchospasm, and the relief afforded by the bronchodilator drug is probably mostly from the relief of the bronchospasm, although the vasoconstrictor element of the drug may be of some importance Fibrosis with loss of lung elasticity favors retention of secretions in the lungs, enhances irritation of bronchial mucosa and predisposes to bronchospasm with defective aeration of alveoli, especially in those cases in which there is considerable impairment of diaphragmatic movement

The hemoglobin was found to be normal in pneumoconiosis (14 to 15 Gm. based on oxygen capacity measurements on the Van Slyke), an elevation of hemoglobin indicating the presence of a cardiac factor (Table 1). In the absence of cardiac failure, polycythemia is not a factor in pneumoconiosis even in cases with obvious cyanosis and emphysema The

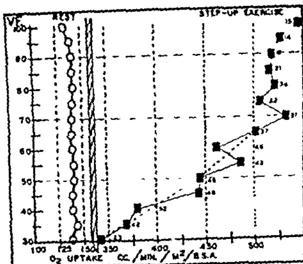


Fig 4—Correlation between the ventilation factor (VF) and the oxygen uptake at rest and during step-up exercise The number of cases for each group is shown by the small figures to the right of the black squares on the graph, and the 15 groups were based on the VF per cent as described for Figure 1 The resting oxygen uptake was normal for all groups A reduced exercise oxygen uptake indicates an inability to increase the pulmonary blood flow corresponding to the degree of exercise given when the ventilation is adequate Note the marked decrease in exercise oxygen uptake in the severe emphysema groups (VF, 30 to 40 per cent)

ether circulation time (arm-to-lung) and the decholin circulation time (arm-to-tongue) are normal in pneumoconiosis, even including those cases with severe degrees of pulmonary emphysema (Table 1) An abnormal ether or decholin circulation time indicates cardiac inadequacy. The total blood volume and the plasma blood volume, as measured by the Evans blue dye (T-1824) and using arterial blood, are also normal in pneumoconiosis in the absence of cardiac failure If the exercise arterial blood pH decreases significantly below the normal level, to 7 35 or below, a cardiac factor should be suspected If the dyspnea time following exercise is out of proportion to the decrease in the ventilation factor, or if the dyspnea is of a profound exertional type, a cardiac factor is usually indicated

A complete history, physical examination and radiologic study provide important information for the clinical evaluation of impairment, however, such information frequently proves inadequate for an accurate

TABLE 3 —*Studies on the Arterial Blood Oxygen Saturation in Asbestosis*

Case	I	II	III	IV	V	VI	VII	VIII
Years of exposure as an asbestos worker	37	30	11	12	15	15	25	17
Total lung capacity, supine % of predicted	74.1	76.8	68.0	61.4	48.6	94.0	93.2	87.6
Total vital capacity, standing, % of predicted	69.5	67.2	61.1	64.4	48.7	99.3	73.3	101.3
3 sec forced expiratory capacity % of predicted normal vital capacity	56.8	56.4	56.8	63.9	48.2	95.6	67.7	98.5
Arterial Blood Oxygen Saturation Per cent								
Rest, air	93.8	92.7	88.4	96.7	96.1	95.1	94.0	95.0
Rest, IPPB, air	96.5	—	90.5	—	96.8	97.0	98.2	98.0
Rest, 30% O_2	—	98.8	—	—	97.8	—	98.0	99.0
Rest, 100% O_2	99.6	100.0	98.9	100.0	99.6	98.6	99.2	100.0
Exercise, air	82.0	85.0	78.0	92.0	93.0	87.2	92.7	91.2
Exercise, 30% O_2	90.5	92.8	85.6	93.6	94.2	91.6	94.6	95.2
Exercise, IPPB, Air	89.5	87.4	—	—	—	—	—	—

IPPB = intermittent positive pressure breathing on air
Exercise = one minute, step-up on 8 in stool
Diagnosis of asbestosis made on basis of history, x ray appearance of chest and the demonstration of asbestos bodies in a few cases

blood when elevated in pneumoconiosis is a very significant measurement and usually indicates the presence of severe emphysema However, a normal or decreased carbon dioxide content does not indicate the absence of emphysema The direct tension measurement of the arterial Pco_2 and the CO_2 content have been found to be the best reference guides of the adequacy of alveolar aeration If the arterial CO_2 is elevated, this indicates an inadequate alveolar aeration, but since emphysema develops slowly, the arterial pH may be in the normal (compensated) range (TABLE 1). In our experience, the only accurate way to detect the presence of acute respiratory acidosis is to measure the arterial blood pH on a glass electrode pH meter A poor correlation of the arterial CO_2 content and the Pco_2 with the pH has been found in severe emphysema The calculated Pco_2 and pH values have been found to be inaccurate in pneumoconiosis where a severe degree of pulmonary insufficiency exists

There was no apparent correlation of pulse and respiration rate and the severity of the pulmonary function impairment (TABLE 1). A lack of correlation was also noted for the minute ventilation measurements except in the group with a far advanced degree of pulmonary function impairment, where a significant reduction was present during exercise Studies on the expired air revealed normal oxygen uptake and a slight to moderate decrease in the per cent of oxygen extracted from the inspired air (TABLE 1) During exercise, the oxygen uptake was reduced in a moderate to marked degree especially in those cases with severe emphysema, and the per cent of oxygen extracted from the inspired air decreased in a moderate degree The exercise oxygen uptake has been found to be well correlated with the ventilation factor in pneumoconiosis (TABLE 1, FIG. 4), whereas the per cent of oxygen extracted from the inspired air with exercise frequently shows no significant correlation. Since an adequate minute ventilation and pulmonary blood flow are the two factors necessary to remove from the lung an amount of oxygen corresponding to the degree of exercise given, when the ventilation is adequate and the oxy-

the ventilation factor had nodular-confluent changes, there were 14 cases with a normal ventilation factor and nodular-confluent x-ray changes There was no significant correlation of the x-ray changes with the ventilation factor (Fig. 5). Similar comparisons for the forced expiratory capacity for three seconds ($FEC_{3.0}$), the maximal breathing capacity and the residual air as per cent of normal predicted failed to reveal any significant correlation. Thus, the presence of extensive changes on the x-ray is not necessarily associated with a decrease in the $FEC_{3.0}$ or the maximal breathing capacity below the normal predicted value. Also, the residual volume may be normal in the presence of nodular and confluent x-ray changes Similar observations were noted as in coal miners of the lack of correlation between the x-ray changes and the severity of the function impairment (Table 5). The degree of pulmonary function impairment was classified as normal, slight, moderate or severe based on the battery of tests described [15] In the group of 98 workers, 30 were classified as normal, 48 with a slight degree, 14 with a moderate degree and only 6 with a severe degree of pulmonary function impairment (Table 5). In the group with normal function, 16 had negative x-rays, 9 had linear-nodular changes and 5 had nodular-confluent changes In the group with a slight degree of function impairment, the x-ray changes were classified as: 20 negative, 18 linear-nodular and 10 nodular-confluent In the group with a moderate degree of function impairment, 5 were negative, 5 linear-nodular and 4 nodular-confluent In the 6 cases with a severe degree of function impairment, one had linear-nodular changes and 5 nodular-confluent In a similar manner, no significant correlation was noted between the exercise arterial blood oxygen saturation and the x-ray stage and the age of the diatomite worker.[21] In a previous report on 11 cases of diatomite pneumoconiosis with clinical symptoms of disability, the function changes were typical of severe emphysema and fibrosis.[16] Heating crude diatomaceous earth changes amorphous silicon dioxide to crystalline cristobalite, a silicosis producing substance, and exposure to this dust has resulted in marked pulmonary insufficiency in some cases before dust control measures were instituted.[25]

Table 5.—*Correlation of the Degree of Pulmonary Function Impairment and Roentgenologic Classification in 98 Diatomite Workers*

Roentgenologic Stage*	Degree of Pulmonary Function Impairment†				
	Normal	Slight	Moderate	Severe	Total
Negative	16	20	5	0	
Total all cases negative					41
Linear-nodular					
first stage	7	12	5	0	
second stage	1	2	0	0	
third stage	1	4	0	1	
Total linear-nodular cases	9	18	5	1	33
Nodular-confluent					
nodular second, confluent first	3	2	1	0	
nodular third, confluent first	0	2	0	0	
nodular second, confluent second	2	3	1	3	
nodular third, confluent second	0	3	2	2	
Total nodular confluent cases	5	10	4	5	24
Total, all cases	30	48	14	6	98

* X-ray classification of U S Public Health Service

† Over-all evaluation based on complete battery of tests as described Dis Chest *24:* 378 (Oct) 1953.

In Table 6 data are presented on four types of disabling pneumoconiosis In Cases I, II and IV there is obstructive emphysema and impairment in intrapulmonary mixing In the asbestos case, the obstructive element is absent and emphysema is not a significant factor in the disability, but the restrictive condition is dominant and this individual cannot take a deep breath The maximal breathing capacity is much greater in Case III than the $FEC_{3.0}$ as per cent of predicted Intermittent positive pressure breathing of air improved the resting saturation in all 4 cases The decrease in the exercise saturation was not corrected by high oxygen breathing (32 to 40 *per cent oxygen*) for Cases I, III and IV, and this indicates the

TABLE 4.—*Correlation of Pulmonary Function Studies and Roentgenologic Classification of Pneumoconiosis in 600 Coal Miners*

	No Cases	Roentgenological Stage*			
		N-B	1st	2nd	3rd
Degree of function impairment†					
slight	85	10	16	28	31
moderate	163	15	21	35	92
severe	173	10	20	25	118
very severe	79	2	16	15	46
Degree of pulmonary emphysema†					
none	37	6	3	13	15
slight	136	8	18	35	75
moderate	164	13	19	23	109
severe	108	7	19	19	63
very severe	55	3	14	13	25

* N, normal, B, borderline, increased peribronchial markings, first stage, slight fine mottling of parenchyma and increased size and density of hilar lymph nodes, second stage, typical nodular round and oblong shadows of soft, even density from 2 to 6 mm in diameter, third stage, shadows more than 6 mm in diameter and coalescence forming aggregates

† Over-all evaluation based on complete battery of tests as described Dis Chest *24* 378 (Oct) 1953

determination of the extent of the disability present, and in some cases even fails to indicate the nature of the respiratory difficulty In recent years, the discrepancy between roentgenologic findings and pulmonary function studies in the appraisal of disability in pneumoconiosis has become well recognized in many parts of the world. In our studies, no apparent correlation has been found between the roentgenologic stage of pneumoconiosis and the degree of pulmonary function impairment in coal miners (TABLE 4).

Pulmonary function studies have been obtained on 98 diatomaceous earth workers still on the job in this industry and without major complaints [21] The workers were selected by the United States Public Health Service in connection with their survey of the diatomite industry[1] to provide a representative cross section of this type of pneumoconiosis. The x-ray classification used by the Public Health Service, described findings as normal, linear-nodular and nodular-confluent The linear and nodular changes were grouped together, and the classification was simplified as indicated below:

LN_1 suspicious for linear-nodular changes

LN_2 definitely abnormal linear changes, nodular changes, or both, involving an area less than the equivalent of two quadrants of the lung field

LN_3 linear changes, nodular changes, or both, involving more than one half of the total lung area of extending to or nearly to the periphery of both lung fields bilaterally

C_1 confluent shadows of uncertain or ambiguous significance, superimposed on any of the foregoing

C_2 massive confluent opacities definitely present, extending over less than the equivalent of three anterior rib spaces on either side

C_3 massive confluent opacities definitely present, extending over the equivalent of three or more anterior rib spaces on either side

C_4 massive confluent opacities, associated with gross distortion of the pulmonary anatomy

The ventilation factor as per cent of the normal predicted value was correlated with the x-ray change and the age of the individual[21] (FIG 5) In 41 cases, the ventilation factor was 100 per cent or above of predicted and in 32 very slightly decreased (not of significant degree), and this would indicate that in 73 of the 98 cases studied alveolar aeration was normal. In 14 cases, the ventilation factor was decreased slightly (80 to 90 per cent) and in 11 cases moderately (60 to 80 per cent). Although 7 of the 11 cases with a moderate decrease in

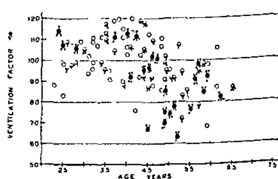


FIG 5.—Correlation of the ventilation factor as per cent of predicted normal with age in years and x-ray appearance in 98 subjects still working in the diatomite industry The number of dots attached below the circle indicates the stage of nodularity on the x-ray (1, 2 or 3), and the number of dots above, the degree of confluent change (1, 2, 3 or 4) The open circles indicate negative x-rays There was no apparent correlation of the ventilation factor and the x-ray change.

perfusion of blood through nonventilated areas, rather than the existence of alveolar-capillary membrane blocks.[10] The coal miner case illustrates a frequent finding in this type of pneumoconiosis, the dominant aspect of fibrosis with emphysema secondary. In Cases I and IV, the emphysema is dominant to the fibrosis, and in Case III the fibrosis is primary with emphysema insignificant. The exercise oxygen uptake was markedly decreased in all cases, indicating the inability to expand in a normal manner the pulmonary vascular bed and the presence of increased pulmonary vascular resistance. The data presented on the 4 cases (Table 6) suggest that the exercise cardiac output is low.

In an attempt to provide subjective relief to individuals disabled from the fibrosis and emphysema of pneumoconiosis, intermittent positive pressure breathing (IPPB) has been used as a new type of therapy designed to counteract the pathologic alterations produced by the fibrosis and emphysema.[14] The IPPB therapy has been combined with the simultaneous nebulization of a potent bronchodilator drug, such as Vaponefrin or Isuprel, also antibiotics, wetting agents and more recently humidification. The IPPB treatments promote bronchial drainage, provide a more uniform distribution of the aerosol (thus increasing the effectiveness of the medication) and provide a breathing exercise improving muscle tone.[14] Digitalis, aminophylline and diuretics are probably the most useful drugs in the treatment of cardiac complications in pneumoconiosis. Aminophylline and oxygen are most useful in treating the increased pulmonary vascular resistance. Potassium iodide and ammonium chloride may be used as expectorants. Steroid therapy properly supervised may be helpful in cases with severe bronchospasm and cases with fibrosis as a dominant feature. In order to obtain the maximal benefits possible from the use of the IPPB treatments, patients with severe emphysema and fibrosis need a unit for use at home where the pressure breathing treatments can be taken for an extended period of time (in most severe cases a unit will be needed indefinitely). The use of 40 per cent oxygen with the IPPB is recommended for most cases. Early observations indicate that in some cases, even in severe emphysema, the progress can be arrested with adequate pressure breathing therapy. Most patients are able to increase their activity after the treatment, some to a striking degree, but in a small number negligible or no changes occur. In order to properly evaluate IPPB therapy, it is imperative that physiologic measurements be made to assess accurately the degree of pulmonary emphysema, to select patients for whom the treatment is indicated on a long-range basis, and by follow-up studies to evaluate the effectiveness of the treatment. In many cases, IPPB was not recommended because the residual volume was not increased (emphysema was not a significant factor in at least 30 per cent of the cases of coal miners' pneumoconiosis studied even though there were pulmonary complaints). Since these individuals were able to take fairly deep breaths, bronchodilators could be given by any of the conventional methods as indicated for treating bronchospasm. The best treatment for pneumoconiosis is prevention by dust control to prevent dust inhalation. This aspect requires constant study and monitoring on the part of industry. The value of aluminum in prevention is controversial, and definitive proof is lacking. The use of aluminum dust prophylactically is no substitute for dust control.

Summary

The extent of the impairment of pulmonary function from inhalation of silica or other mineral dusts as silicates, asbestos, carbon, smoke, coal, alumina abrasives, iron or chalk requires pulmonary function measurements with adequate tests to evaluate (1) the ventilatory status, (2) the transport of oxygen and carbon dioxide in the lungs and (3) pulmonary blood flow. Single tests of lung function or tests of only one aspect are unsatisfactory. The presence of x-ray changes constitutes no cause for removing the worker from the job as demonstrated in the 98 diatomite workers studied. No further progression may occur with improved dust control in the plant. If serial follow-up studies of pulmonary function reveal significant progressive changes, then

TABLE 6 —*Pulmonary Function Measurements in 4 Types of Pneumoconiosis with Severe Function Impairment*

Case No	I	II	III	IV
Age, Yr	55	61	58	57
Height, cm	176 5	172 0	156 2	165 1
Vital capacity supine				
ml observed	2265	3640	1835	2620
% predicted	52 1	95 4	56.8	70 4
Three second forced expiratory capacity				
ml observed	1391	1780	1837	1989
% predicted	32 0	46 7	56 8	53 5
Maximal breathing capacity L /min.				
observed	25 6	31 4	80 2	34.2
% predicted	21 9	26 7	73 7	32 4
After bronchodilator L /min				
observed	33 1	36 2	104 0	43 1
Alveolar N_2 after 7 min O_2 breathing	2 78	2 78	1 22	6 26
Residual air				
ml observed	3210	2094	1359	3288
% predicted	221 4	128 1	126 1	265 2
Total lung capacity				
ml observed	5475	5734	3194	5908
% predicted	94 4	105 2	74 1	119 1
Residual % of total lung capacity	58 6	36 5	42 5	55 7
Ventilation factor, %	32 2	51 0	63 1	43 6
Arterial blood oxygen saturation %				
rest-air	89 5	95 0	93 8	91 6
rest-IPPB, air	91.0	97 3	96 5	95.7
rest-100% O_2	97 3	—	99.6	99.2
exercise-air	83 7	85 8	82 0	90 5
exercise-IPPB, air	—	—	89 5	—
exercise-32% O_2	—	—	90 5	94.0
exercise 40% O_2	92 2	—	—	—
CO_2 content vol %				
rest	60.3	52 0	45 5	48.5
exercise	56 9	49 9	45 8	44 9
Min Vent L /M²/BSA				
exercise	8 14	9 11	10 0	12 1
Oxygen uptake, ml./min /M²/BSA exercise	331	339	403	314

Case I—Diatomite worker three years (x-ray, nodular third, confluent third).
Case II—Hard coal miner 37 years (x-ray, third stage)
Case III—Asbestos Worker 37 years (x-ray, linear changes, accentuated at both bases).
Case IV—Hard rock miner 25 years (x-ray, second stage).

Alveolar Hypoventilation

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Introduction

ALVEOLAR hypoventilation is the result of respiratory failure. It can be acute or chronic There may be an association with pulmonary disease, deformity of the thorax or with central nervous system disorders The presence of alveolar hypoventilation should lead to a search for the precise cause. The concept of cardiac failure is well understood; and the concept of respiratory failure should be equally well understood. The function of the lungs is to oxygenate the blood and eliminate carbon dioxide from the blood, and with inadequate function the lungs will fail. One of the important mechanisms which participates in this function is ventilation or more specifically "alveolar" or effective ventilation. Methods for measurement of alveolar ventilation are described in Chapter 38 Rational therapy of the patient with lung disease depends on the recognition and correction of insufficient alveolar ventilation

Definition

The lungs are hypoventilated when ventilation is insufficient to maintain alveolar P_{O_2} and P_{CO_2} at normal levels. With normal or increased minute volume of ventilation, hypoxemia can occur without hypercapnia in patients with either cardiac or pulmonary disease Increased arterial P_{CO_2}, however, is the inevitable result of hypoventilation of the lungs as a whole. Elevation of P_{CO_2} rarely results from primary cardiac failure

Etiology

There are many causes of hypoventilation. The excellent classification of Comroe, Forster, DuBois, Briscoe and Carlsen[10] is as follows: (1) depression of the respiratory centers, (2) interference with neural conduction or with neuromuscular transmission to the respiratory muscles, (3) diseases of respiratory muscles, (4) limitation of movement of thorax, (5) limitation of movement of lungs and (6) parenchymal pulmonary diseases These categories will be discussed in this order.

1. *Depression of the respiratory centers.* This most frequently occurs during anesthesia. The anesthesiologist recognizes this and assists the patient's ventilation. In spite of this assistance, many patients are hypoventilated either during[15] or shortly after the operative procedure is completed [15]

Under some circumstances, morphine and barbiturates may depress the respiratory center and can cause hypoventilation. The patient who has taken a large dose of barbiturates rapidly develops respiratory insufficiency because of upper airway relaxation or constriction, plus respiratory center depression. This patient needs adequate ventilation. This requires the introduction of an oropharyngeal or endotracheal tube and manual or mechanical assistance of ventilation until the depressant effect of the drug has been dissipated.

Idiopathic damage to the respiratory center has been reported by Ratto, Briscoe, Morton and Comroe[21] and by Richter, West, and Fishman [23] The two patients had extensive cardiac and pulmonary studies No evidence of heart disease or lung disease was found. Both patients were found to have hypoxemia, hypercarbia and polycythemia Both were capable of increasing arterial oxygen saturation to normal and decreasing arterial P_{CO_2} to normal by voluntary hyperventilation. Ratto et al. postulated that in their patient medullary respiratory center depression might be postencephalitic or secondary to thromboses in the

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the worker should be removed before total disability occurs There is great need for more extensive application of accurate pulmonary function testing in industry

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inhalation of CO_2. But this diminished response continued even though the arterial blood carbon dioxide tension and alkali reserve were restored to normal by prolonged therapy including the use of acetazolamide.[12] Cherniack and Snidal[7] have shown that obstruction to breathing causes a diminished response to inhalation of CO_2. The issue of whether or not there is respiratory center depression in emphysema needs further study.

Other possible causes for depression of the respiratory center include cerebral trauma, increased intracranial pressure and cerebral ischemia.

2. *Interference with neural conduction or neuromuscular transmission to the respiratory muscles* This can occur in traumatic spinal cord lesions, in infections, such as poliomyelitis and tetanus, in peripheral neuritis, e g, infectious neuronitis, and in neuromuscular block produced by neuropharmacologic agents, e g, curare, neomycin, decamethonium, succinylcholine and nerve gases, myasthenia gravis, botulinus or nicotine poisoning Lukas and Plum[19] studied patients with respiratory paralysis convalescing from acute poliomyelitis and found reduction in vital capacity, increase in the residual volume, some decrease in the maximal breathing capacity, normal distribution of inspired air and normal alveolar capillary P_{O_2} gradient Hypoventilation occurred in 5 of 12 patients They emphasize that slight but important degrees of paralysis may not be recognized In addition to paralysis, many such patients have diminished compliance of the lungs and of the thoracic cage The physician must be alert to the possibility of alveolar hypoventilation in these patients

3. *Diseases of the respiratory muscles* There are a few reports of primary muscle disease leading to alveolar hypoventilation.[4, 17] It is to be expected that such diseases as progressive muscular dystrophy, the myotonias, periodic paralysis, polymyositis, dermatomyositis or diseases characterized by metabolic defects in muscle could produce alveolar hypoventilation because of muscular weakness and secondary infections such as hypostatic pneumonia

4 *Limitation of movement of the thorax.* Chapman, Dill and Graybiel[6] described changes in the lungs resulting from deformities of the chest, and more recently Fishman, Bergotsky, Turino, Jameson and Richards[11] have described respiratory changes secondary to kyphoscoliosis These patients may develop alveolar hypoventilation The mechanism appears to be limitation of the movement of the chest wall Similarly, scleroderma can cause severe restriction of chest wall movement

5 *Limitation of movement of the lungs.* This can occur in patients with greatly thickened pleura Such a patient has been reported by Coates, Brinkman and Noe.[8]

6. *Pulmonary diseases.* Any disease of the lung can lead to alveolar hypoventilation provided there is sufficient mechanical change in lung tissue. Pulmonary emphysema in failure is the most common. Any one of the infectious diseases in the lungs which causes enough mechanical alteration of lung tissue, either through destruction or infiltration, can lead eventually to alveolar hypoventilation. Extensive irradiation of the lungs results in pulmonary fibrosis and can eventually result in alveolar hypoventilation

Characteristics

The physiologic characteristics of alveolar hypoventilation are an increase in the arterial and alveolar P_{CO_2} and a decrease in alveolar and arterial P_{O_2} There are no specific clinical characteristics, although careful observation should reveal diminished breath sounds and decreased or imperceptible movement of air at the mouth.

Clinical Symptoms

The patient with alveolar hypoventilation need not have any specific symptoms The most common are weakness, somnolence, cyanosis and dyspnea Secondary polycythemia may be the presenting observation[2] Somnolence has been observed in a number of patients, but somnolence can occur without alveolar hypoventilation, and alveolar hypoventilation occurs in the absence of somnolence. Signal elevation of carbon dioxide tension is generally considered to be associated with cerebral depression and terms such as "carbon dioxide narcosis" are popular, generally accepted and

region of the respiratory center, since patients with polycythemia vera are well known to have a tendency toward vascular thrombosis Richter et al. had no explanation for the presence of respiratory center depression in their patient. Rodman and Close[25] reported a patient they believed had idiopathic respiratory center depression. They failed to exclude convincingly pulmonary vascular disease. There are patients who do develop respiratory center depression as an isolated disturbance. In some, the precise mechanism of respiratory center involvement is not known Possibilities include toxic changes in the center, vascular changes near or in the center, new growths invading the area of the center, and residua of infectious diseases in the medulla

Newman, Feltman and Devlin[20] reported 5 patients with "polycythemia vera," two of whom had alveolar hypoventilation These two may have had isolated respiratory center depression as the cause of hypoventilation The suggestion has been made that polycythemia vera can lead to thrombosis in the area of the respiratory center and consequent respiratory center depression Such a cause has not been substantiated by pathologic studies The bulk of the evidence in patients with polycythemia vera indicates that they have normal arterial oxygen saturation and carbon dioxide tension unless they have heart disease or lung disease.

Recently, a great deal of interest has been aroused by the observation of alveolar hypoventilation and polycythemia in patients with extreme obesity Burwell, Robin, Whaley and Bickelmann[5] have given the picturesque name "Pickwickian syndrome" to this combination of signs and symptoms The basic physiologic defect is alveolar hypoventilation There is no agreement as to what initiates alveolar hypoventilation in these persons Bedell, Wilson and Seebohm[3] found that alveolar hypoventilation in obese individuals was associated with myxedema or lung disease. That obesity alone is enough to produce respiratory center depression has not been established

Kaufman, Ferguson and Cherniack[16] found increased oxygen cost of breathing in obese persons. They suggest that in the obese patient the increased oxygen cost of breathing is caused by an increase in the elastic resistance of the thorax They indicated that there may be a relationship between the oxygen cost of breathing and the arterial P_{CO_2}. Gilbert, Sipple and Auchincloss[14] believe that hypoventilation is best explained by a defect in respiratory control They assess respiratory control by measuring the ventilatory response of patients to breathing a mixture of 5 per cent carbon dioxide in air They found no correlation between separately determined oxygen cost of breathing and sensitivity of the respiratory center and conclude that obesity places a stress on respiratory control and that it is independent of increased work of breathing. There is a question of interpretation here, since failure of a patient to respond normally to breathing a mixture of 5 per cent carbon dioxide may be caused by a defective chest wall musculature, airway obstruction[7] or reduced sensitivity of the respiratory center The test does not distinguish between these mechanisms The alveolar hypoventilation which develops in obese subjects in whom lung disease has been completely excluded, has been attributed to an excessive load on the respiratory muscles Such an explanation is reasonable but not certain. Since the process was reversible when the patients lost weight,[3] no permanent damage had been done to the respiratory center

Wilson and Bedell[28] found that myxedema alone does not produce alveolar hypoventilation The association of myxedema with obesity may produce alveolar hypoventilation. The precise mechanism of alveolar hypoventilation is this situation is unknown, although the most probable explanation is that there is interference with neural conduction or with neuromuscular transmission to the respiratory muscles It may be caused by actual involvement of the respiratory muscles by the myxedema plus limitation of movement of the thorax and diaphragm from obesity

In various clinical states, characterized by carbon dioxide retention, there may be respiratory center depression. Formerly, pulmonary emphysema was thought to be an example. It has been demonstrated[1, 12, 26] that patients with pulmonary emphysema and carbon dioxide retention have a diminished response to

about 1 L. of 8 per cent CO_2 in a bag to obtain equilibrium between alveolar air and mixed venous P_{CO_2} appears to be a more dependable method for precisely evaluating hypoventilation.[9]

Treatment

The treatment of the patient with alveolar hypoventilation seeks to provide adequate ventilation and eliminate carbon dioxide from the blood The precise method for doing this depends on the nature of the patient's disease. In patients with primary lung disease, e g., bronchial asthma, treatment of the basic disease may help restore alveolar ventilation to within normal limits. In other situations such as tetanus, poliomyelitis, infectious neuronitis and drug depression, restoration of adequate ventilation may tide the patient over his acute illness These diseases are frequently fatal when alveolar hypoventilation is not recognized or treated.

Oxygen is a helpful but dangerous and frequently misused agent in patients with alveolar hypoventilation It is helpful because arterial P_{O_2} can be restored quickly to normal or higher than normal levels. It is dangerous because when arterial P_{O_2} is restored to normal, the hypoxemia stimulus to respiration is gone and already dangerous hypoventilation may be made worse. It is misused by persons who regard hypoventilation as inadequate saturation of arterial blood with oxygen but forget carbon dioxide retention

A few remarks are in order in regard to the use of artificial methods of increasing alveolar ventilation or maintaining it at an adequate level. The most generally available method is mouth-to-mouth breathing. Next would be manual assistance of ventilation by bag and mask or bag and endotracheal tube, as used by the anesthesiologist When the situation requires long-term artificial ventilation, respirators are generally used. When the lungs are normal, any one of several devices is satisfactory. The Drinker-type respirator will provide adequate minute volume of ventilation for most patients. The use of this type of respirator is most successful in patients who have infrequent or very feeble breathing efforts of their own. Patients still capable of producing forceful breathing efforts have great difficulty in adjusting their natural respirations to the rhythm of a respirator. The end result may be a poor minute volume of ventilation and actual increase in arterial P_{CO_2}. A further disadvantage of this type respirator is that it sequestrates the patient from physical examination, laboratory examination and nursing care. It makes radical position change of the patient impossible, and thereby sets the stage for the development of hypostatic pneumonia. The intermittent positive pressure respirator is preferable to the Drinker-type, especially for the patient who is making reasonable inspiratory efforts. When the patient makes an inspiratory effort, the demand valve of the positive pressure respirator is opened and a preset volume or pressure of air under positive pressure flows into the patient's lungs. The machine can be set so that an adequate tidal volume is obtained in most cases. Expiration is passive; when mask pressure has fallen to atmospheric and the patient attempts to inspire, the cycle is repeated. This assists the patient in inspiration at the time of the patient's natural inspiration and reduces the work of breathing This machine is potentially dangerous, since arterial hypotension may occur requiring supportive therapy for circulatory impairment. This type of respirator can be used for patients who are not making inspiratory efforts and in those who are. It has the advantage that the patient is accessible to physical examination, laboratory examination and nursing care. Radical position change to avoid hypostatic pneumonia is possible

When mechanical aids to ventilation are utilized, precise measurements of the improvement in volume of ventilation, alveolar P_{CO_2} and arterial P_{CO_2} and oxyhemoglobin saturation are extremely valuable. Blood gas studies are the most reliable means of evaluating results Because mechanical aids to ventilation tend to deliver air to the same parts of the lung each time, efforts to ventilate the entire lung should be made by giving "deep breaths" and by radical position change of the patient. If the patient is unable to cough out the increased secretions that so often result from acute

used erroneously. A sudden rise in carbon dioxide tension usually produces anesthesia, but many patients with chronic carbon dioxide retention are mentally alert Certainly, no inverse proportional relationship between cerebral alertness and carbon dioxide retention has been demonstrated. Similarly, patients with alveolar hypoventilation may or may not have dyspnea. There is no relationship between the severity of dyspnea and the degree of alveolar hypoventilation Dyspnea is a subjective symptom Some patients who have perfectly normal alveolar ventilation are dyspneic Some patients with severe alveolar hypoventilation are *not dyspneic*

It should be emphasized that in certain patients with alveolar hypoventilation the symptoms of alveolar hypoventilation tend to mimic the symptoms of the primary disease For example, in a patient with poliomyelitis, twitching, hypertension, tachycardia, coma and convulsions may be ascribed to the encephalitic stage of the disease. In such a patient, all these signs may be caused by alveolar hypoventilation. If alveolar ventilation is restored to normal, the signs may disappear Another example *is the patient with tetanus who develops the* same signs and symptoms The physician may be comforted by making a diagnosis of cerebral edema, but adequate ventilation may save the patient's life

Diagnosis

Alveolar hypoventilation must be suspected or it will be missed, because it is often subtle in its manifestations. Elevation of arterial P_{CO_2} is the cornerstone of the diagnosis The finding of any one of the following is necessary diminished minute volume of ventilation, elevation of alveolar P_{CO_2} or elevation of arterial blood P_{CO_2}. The present methods of obtaining arterial blood P_{CO_2} require careful analysis of a number of factors or use of a tedious method for direct measurement. One can measure CO_2 content, pH and hematocrit and calculate the P_{CO_2} using a suitable nomogram The bubble-equilibrium method of Riley[27] requires great skill and patience though it also yields P_{O_2}. The new carbon dioxide electrodes which directly measure P_{CO_2} by virtue of its effect on pH may be a step forward in the recognition of alveolar hypoventilation.

Simple methods of measuring alveolar P_{CO_2} have been described, including that of Ravin and Stein.[22] Alveolar and arterial P_{CO_2} were compared in patients by Stein and Colp[27] The patient blows out through an expiratory tube An end-expiratory sample of alveolar air is trapped for analysis in a 50 ml. gas collection chamber This chamber is sealed, an ampule of 2 N sodium hydroxide is broken in the chamber. This liquid absorbs the carbon dioxide in alveolar air and creates a partial vacuum which can be read directly in terms of P_{CO_2} from an aneroid gauge attached to the chamber. However, obtaining a representative sample of alveolar gas in a somnolent patient with emphysema presents a major problem. Another quick method of estimating the presence of alveolar hypoventilation is to measure alveolar P_{CO_2} using an infra-red carbon dioxide analyzer. The patient breathes out through the carbon *dioxide analyzer The percentage of* carbon dioxide in the endtidal air is measured and then using the following formula, alveolar P_{CO_2} can be calculated

alveolar CO_2 tension $(P_{A_{CO_2}}) = P_B \times \%\ CO_2$ *in end-tidal air* $\times (P_B - 47)/(P_B - P_{H_2O}{}^*)$

P_B = ambient barometric pressure

P_{H_2O} = water vapor pressure, saturated at the ambient temperature

For example

Barometric pressure (P_B)	= 750 mm Hg
% CO_2 in end tidal air	= 5 2%
Room temperature	= 25 C.
Alveolar CO_2 ($P_{A_{CO_2}}$)	= 750 × 052 × 703/727
tension	= 38 mm Hg

This measurement of alveolar P_{CO_2} is accurate within 3 to 4 mm Hg in most patients without pulmonary disease but may underestimate arterial P_{CO_2} in the presence of uneven ventilation and blood flow This method has the same sampling problem as the chemical analyzer described above It is a satisfactory method for estimating the arterial P_{CO_2} tension in certain circumstances but not always Rebreathing

* The expression $(P_B - 47)/(P_B - P_{H_2O})$, there is a correction factor for condensation of water vapor which occurs during the flow of gas to the analyzer

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respiratory tract infection, tracheotomy may be life-saving It not only permits suctioning the airway but facilitates artificial respiration through the tube.

In patients with lung disease, the treatment should be directed at the lung disease. Alveolar ventilation may be improved through the treatment of infections, the use of bronchodilators, the reduction of upper airway obstruction and instruction in the most efficient way of breathing

The promotion of bicarbonate excretion by the kidney, using carbonic anhydrase inhibitors, may have a favorable influence on carbon dioxide excretion, the sensitivity of the respiratory center and pulmonary vascular congestion by assisting salt and water excretion. The amount of carbonic acid which may be excreted in the urine after administration of these agents is not established, but it is probably not great However, Fishman et al[12] have administered acetazolamide (Diamox) in a dosage of ½ Gm. per day to patients with chronic pulmonary emphysema and have observed a return of arterial blood P_{CO_2} and alkali reserve toward normal

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Section X

PHYSIOLOGIC THERAPY OF PULMONARY DISEASES

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Physiologic Therapy of Bronchopulmonary Diseases

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THE basic dependence of man on the air he breathes has been appreciated since antiquity Recently, the increased use of oxygen and therapeutic gases has been paralleled by the introduction of new modalities for their administration which require understanding of the physiologic basis of treatment as well as familiarity with the apparatus itself Basically, all these newer devices attempt to correct oxygen deficiency, carbon dioxide overproduction or retention, or combinations of these This brief discussion can only attempt to highlight the subject, and the reader should review the individual manufacturer's specifications and directions before using each piece of equipment

Therapeutic Gases

Oxygen

Many hospitals now enjoy the advantages of piping systems for oxygen, thus eliminating the more cumbersome transportation of individual oxygen cylinders A central bank of manifolded oxygen cylinders or a large reservoir of liquid oxygen provides the source of supply, and the size of the unit installed can be varied to the volume needs of individual users The line pressure is reduced at the source, and the gas is then piped throughout the building, arriving at the various outlets at a pressure of 50 pounds per square inch Individual oxygen cylinders are still in wide use; the most popular is the "H" type which contains 6,800 L (244 cubic feet) of oxygen and supplies roughly 14 hours of gas at a flow rate of 8 L per minute The smaller "D" and "E" type cylinders provide 45 and 70 minutes of service, respectively, at a similar flow rate and are principally used for emergencies, as well as the movement of hypoxic patients from place to place within the hospital

Carbon Dioxide

The principal indications for therapy with carbon dioxide at present are the treatment of hiccoughs[7, 12] and liquefaction of tenacious sputum[5] Its use for the production of hypercapnea has become less frequent Carbon dioxide should not be administered as a respiratory "stimulant" in states in which respiratory acidosis is already present This gas is supplied for medical use in cylinders containing oxygen admixtures, ranging from 5 to 10 per cent carbon dioxide and 95 to 90 per cent oxygen The use of undiluted carbon dioxide from cylinders supplied for industrial or laboratory purposes is hazardous because of the danger of inadvertent administration of excessive doses

Helium

This inert gas is commonly supplied in a number of different combinations with oxygen, the most popular mixture containing 80 per cent helium and 20 per cent oxygen The lighter mass of helium (about one-seventh the density of air) insures a great reduction in turbulent resistance involved in ventilation while laminar resistance is unaffected Helium is chiefly indicated in the treatment of obstructive laryngeal and tracheobronchial disease in which local turbulent flow is a problem This is discussed at length in Chapter 37. Helium-oxygen mixtures require a closed system,

such as a tight-fitting mask and reservoir bag. A tent or nasal apparatus should not be employed since the mixture cannot be maintained at the desirable composition for effective therapy A cylinder regulator or central piping system flowmeter specifically calibrated for helium-oxygen use is required; the flow of an 80/20 mixture which is actually delivered and the reading on a meter calibrated for oxygen could not correspond because of the different densities of the respective gases As an approximation, one may calculate the 80/20 mixture as flowing at a rate 1 7 times that indicated on the oxygen flow meter.

Oxygen Regulators

When oxygen cylinders are used, one or two stage regulators are employed to reduce cylinder gas pressures to safe levels. The single stage regulator accomplishes this in one step, with the delivered gas metered by a flow control valve. Constant adjustment is necessary with this type of regulator as cylinder pressures fall, if uniform delivery is to be assured. The first portion of a two stage regulator acts as a reducing valve and lowers the entering gas pressure down to that which can then be passed through the second regulator, or flowing area. Only a single stage regulator (flow indicator) is necessary with central piping systems since the gas arrives at the wall outlets at a reduced pressure. The single stage regulator is usually calibrated to register the flow in liters per minute over a range from 0 to 15 L., and is generally referred to as a liter gauge.

There are two principal varieties of liter gauges, the Bourdon (round) type (Fig. 1A), and the Thorpe (tube) type (Fig 1B); the latter is commonly known as a flow meter. Both measure gas flow, but by different means The Bourdon liter gauge is accurate between flows of 3 and 7 L per minute, with errors on

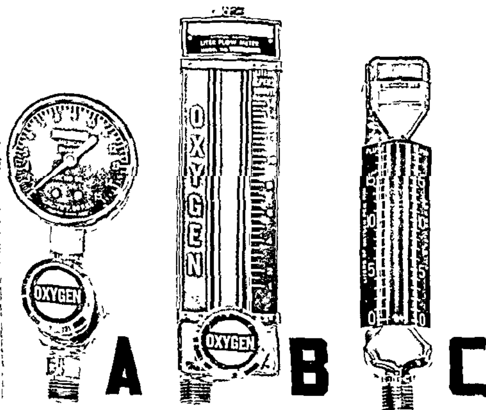


Fig 1—Bourdon (A), Tl (B), and pressure compensated flow meters (C)

either side of those rates reaching 10 per cent. This type is the most versatile, particularly when an "air injector" (oxygen diluter) is used The Thorpe tube flow meter is considered accurate at any reading provided there is unobstructed flow. It utilizes a moving float or ball to indicate the particular flow rate. Since the tube is calibrated on the basis of an unobstructed oxygen flow leaving the flow meter, any obstruction to the free flow of gas develops an appreciable back pressure which alters the reading This difficulty may be obviated by utilizing a back pressure compensated flow meter (Fig. 1C) which indicates true liter flow even when combined with restrictive equipment such as concentration meters, nebulizers and humidifiers For this reason, the back pressure compensated flow meter is probably the most desirable for new installations

Methods of Administration

A variety of methods is available for administration of oxygen over the wide range of concentrations employed for the correction of hypoxic states The technic and oxygen concentration to be provided are determined by the disease present and its complications, as well as the degree of hypoxia Many patients with chronic pulmonary disease need only 35 to 40 per cent oxygen concentration, but in some cases of severe cardiovascular disease, concentrations approaching 100 per cent are usually recommended The principal modalities of administering oxygen are outlined in Table 1

Nasal Catheters

Nasal catheter (Fig 2H) administration of oxygen is frequently used, particularly when more modest concentrations of oxygen are sufficient. In this technic, the tip of a soft plastic or latex rubber catheter (size no 10 or 12 French) designed for oxygen therapy is lubricated with a water-soluble jelly, and inserted into the nostril until the end lies immediately below the tip of the uvula; an oxygen flow of 3 to 4 L. per minute is provided during the insertion of the catheter. Average alveolar concentrations of oxygen as high as 38 per cent may be obtained at flow rates of 6 to 7 L per minute; concentrations 2 to 3 per cent lower are obtained with positioning of the catheter in the nasal pharynx Humidification of the delivered oxygen is mandatory to prevent dehydrating effects on the mucous membranes The technics for providing humidification will be discussed later in this chapter.

Proper use of the nasal catheter requires meticulous attention to detail. Gastric dilatation may result if the tip is positioned too low in the oropharynx; accurate placement may be ensured by direct inspection. Even with proper positioning, oxygen may stream into the hypopharynx and esophagus, if the oral cavity is completely or partially occluded with blood or from trauma The catheter should be alternated from one nostril to the other at 8 hour intervals, at which time a fresh catheter should be used. The humidifier, connecting tubing and the oxygen flow rate should be checked frequently and the patient questioned concerning possible local sensations of irritation or discomfort

Nasal Cannulae (Fig 2G)

Nasal cannulae provide the most comfortable and convenient method for prolonged oxygen administration Although alveolar oxygen

Table 1 —*Methods of Oxygen Administration (After M Eckman)*

Type of Apparatus	Dosage Obtainable %	Accuracy of Control	Ease of Handling	Comfort of Patient	Cost of Operation
Catheter	25–40	Fair	Very easy	Poor–fair	Low
Cannula	25–40	Fair	Very easy	Good	Low
Mask	40–95+	Excellent	Very easy	Poor–long period Fair–short period	Low
Pressure mask	40–95+ + pressure 1–6 cm	Excellent	Special care	Poor	Low
Face tent	35–50	Excellent	Easy	Fair to good	Low
Open hood	40–60	Excellent	Some care	Fair to good	Moderate
Tent	25–50	Poor	Special care	Excellent	High

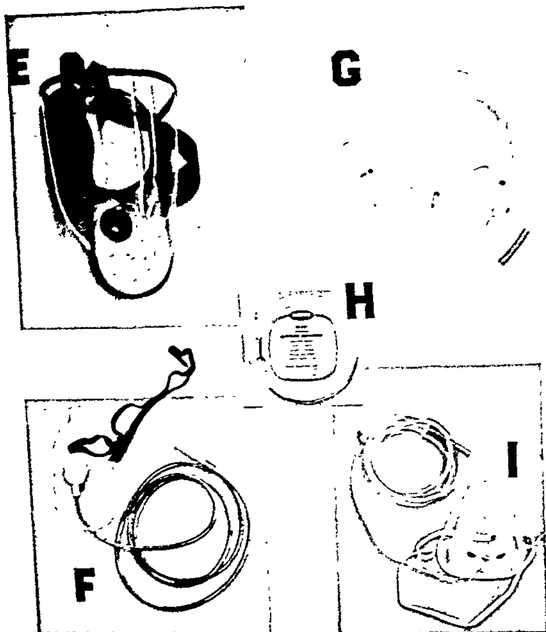


FIG. 2.—Face Tent (E), catheter (H), cannula (G), disposable plastic masks (F, I)

concentrations at similar flow rates are not quite as high as with the nasal catheter, the patient can easily tolerate 8 to 10 L. per minute without complaint, whereas flows in excess of 6 L. per minute with a nasal catheter are often poorly tolerated.[8] The older conjoined metal cannulae have been superseded by newer models consisting of two small plastic tips, about 1 inch long, which fit into the nares so that air flow is not obstructed appreciably. Some manufacturers now provide a convenient, inexpensive, disposable form as a single plastic tube with two small conjoined tips; the cannula device is held in place by an elastic head band which fits firmly below the ears. Water humidification should always be supplied, although the problem of humidification is less severe with the cannula, since the oxygen traverses the nasopharyngeal, mucous membranes in which humidification normally occurs.

Masks

Inhalation therapy by mask has been less popular during the past few years because of

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Open hood	40–60	Excellent	Some care	Fair to good	Moderate
Tent	25–50	Poor	Special care	Excellent	High

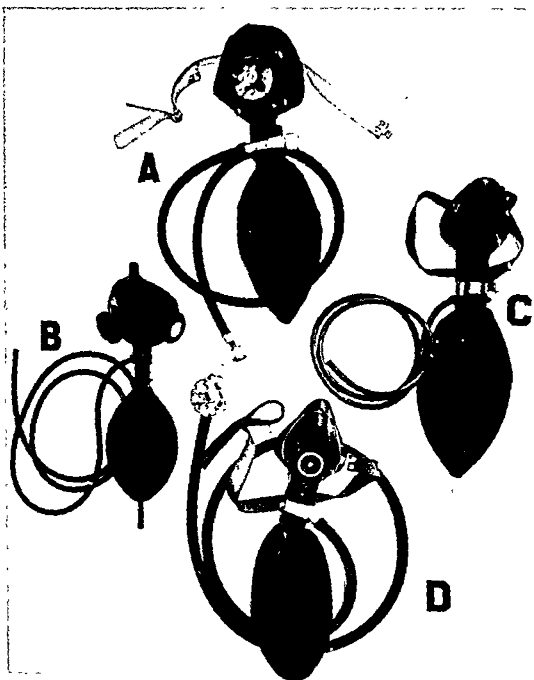


Fig 3.—(A) B E mask with expiratory pressure valve, (B) B.L.B mask, (C) B E mask, and (D) B.E mask with O_2 dilutor

of concentrations of oxygen ranging from 95 to 100 per cent when all apertures are closed, to 40 per cent when the largest aperture is open, the error does not exceed 3 per cent.

When the injector-meter mask is used, the flow of oxygen from the regulator is determined by observing the collecting (reservoir) bag; if it is collapsed at the end of inspiration, a higher flow rate is employed. The operation of the apparatus is watched for several moments, since, in many instances, the pulmonary ventilation surpasses that which is obtained after the patient has breathed an oxygen-enriched atmosphere for several minutes An emergency

patient discomfort during long-term use. An important advantage of this method is the ease with which high oxygen concentrations may be delivered with rapidity Elevated oxygen concentrations provided with mask therapy are particularly valuable in the treatment of cardiovascular emergencies and in subcutaneous emphysema This route of administration is employed extensively by first-aid and rescue squads and for transportation of the urgently ill patient to hospitals

There are three essential characteristics of an adequate mask (1) It must produce a completely, or almost completely, controlled space around the face, and should be well fitted and comfortable, (2) it must be so designed that during inspiration the air breathed will provide the desired oxygen concentration Although it is customary to use an oxygen flow of about 10 L per minute with a mask, instantaneous flow rates determined during certain periods of inspiratory cycling indicate that the velocity during this period may be very much greater. Pneumotachograph data indicate that the maximum instantaneous flow rate may reach 25 L per minute in an adult breathing quietly at 8 L per minute These figures suggest that some type of reservoir must be provided to make up the difference between the flow rate of 10 L. per minute of oxygen and that which the patient requires at any particular instant in his respiratory cycle Such a reservoir may be in the form of a bag from which the patient breathes, or a larger space around the face, as with an open top tent or hoods (3) Carbon dioxide must be prevented from accumulating in the controlled space If a rebreathing bag is employed, the bag must be small, and the oxygen flow in excess of 8 L per minute, or a carbon dioxide percentage of 1 per cent or greater may collect The main purpose of a mask is to produce a controlled atmosphere, and the volume of air reaching the mask must equal the patient's minute respiratory volume This minute ventilation should be noted in each individual patient treated

Masks are often classified as partial rebreathing and reservoir types

1. Many types of rebreathing masks are available, but the new light-weight plastic mask (FIG. 2F) is well tolerated by many patients. The B L B mask (FIG 3B) is the best example of a more permanent type of rebreathing mask The first part of the exhaled gas which contains almost pure oxygen is caught in the rebreathing bag which is located below the face piece of the mask Oxygen flowing through a tube expands the bag to capacity before expiration finishes. The latter part of the exhaled gas contains the highest percentage of carbon dioxide and is forced out through expiratory valves composed of sponge rubber discs and contained in the face piece The patient's next inspiration draws on the mixture in the rebreathing bag; this is now composed partially of the previous exhalation and partially of fresh oxygen If the volume of air in the rebreathing bag is insufficient, air may be drawn in around the face piece and through the emergency inhalation valve, developing a dangerous negative pressure within the chest which can predispose to pulmonary edema Proper maintenance includes regular removal of the sponge rubber discs for cleaning and sterilization, the discs should be replaced only after thorough drying, because wet discs increase resistance in expiration

2 A reservoir bag mask, or meter mask (Barach-Eckman) has a directional valve interposed between the bag and the mask, so that rebreathing is limited to that which occurs within the mask proper The bag serves to collect oxygen during expiration so that it is available during the inspiratory phase of the breathing cycle. A light-weight flutter valve placed in front of the mask, acts as an expiratory valve for the exit of exhaled air The percentage of carbon dioxide in the inspired air does not exceed 0 2 per cent even at flows of 2 L. per minute An air injector is attached to the oxygen regulator and consists of a metal device (FIG 3D) through which oxygen passes into the rubber hose connection to the bag-mask system The streaming of oxygen through the injector exerts a negative pressure which draws in a varying amount of room air, depending on which of a series of progressively graduated holes connects the injector to the outside atmosphere The calibration of these orifices makes possible provision



Fig 4—High humidity tent (hood) with pump to provide pressure source for aerosol generator.

meter allows adequate removal of carbon dioxide at low oxygen flows. Higher oxygen concentrations may be obtained using a 10 L. per minute flow, providing no draft from an open door or window blows across the canopy. Head hoods allow feeding of the patient, care of the head and face, examination and treatment as required, all to proceed without interruption of the supply of oxygen.

Oxygen Tents (Fig 5)

An oxygen tent is a closed apparatus in which the temperature, humidity and oxygen concentration of the circulating atmosphere are all carefully controlled Recirculation of air occurs about 15 times per minute, and cooling is accomplished by passing the oxygen over ice or refrigeration coils; some water vapor is deposited on the coils of the refrigeration unit in the "iceless" types.

With proper technical attention, oxygen tents can provide alveolar oxygen concentrations of approximately 35 to 40 per cent at 12 L and 40 to 45 per cent at 15 L. flow per minute[8] These higher concentrations require substantial amounts of time to develop, e g, it takes about 30 minutes, with a flow rate of 15 L. per minute, to reach the proper concentration in the average tent which contains about 400 L of space In the newer types of tents, with a motor blower recirculating the air, and with oxygen levels determined by a 12 L per minute oxygen flow, carbon dioxide does not accumulate to a significant degree

When tent therapy is prescribed, the canopy should be closed properly to prevent leakage; the oxygen concentration within the tent should be analyzed two to four times daily. The tents should be opened as infrequently as possible. Each time the canopy is opened, the motor blower system should be turned off; when the tent is closed again, the oxygen flow rate should be substantially increased, i e., to 15 L for 5 minutes or more Some of the newer

valve incorporated within the system can provide additional air if the collecting bag is inadvertently collapsed. General comfort is increased by removing the mask periodically so that the patient's face may be washed, dried and powdered.

The B.E mask with the "injector" or air diluter system has the disadvantage that humidification cannot be used with this system. Since adequate humidification is important when prolonged oxygen therapy is being administered, this constitutes a major objection to the air diluter system When low oxygen flows are desired, it would be more desirable to discontinue the tight fitting permanent type mask and substitute (with appropriate humidification) the light-weight and more comfortable plastic mask, the nasal cannula or nasal catheter

Meter Mask with Expiratory Positive Pressure (Fig. 3A)

Designed primarily for the treatment of clinical pulmonary edema, or the edema following gas poisoning, this apparatus is often helpful in managing acute obstructive ventilatory impairment The simple expiratory flutter valve of the meter mask has been replaced by a metal disc with five orifices of various diameters surrounding the flutter valve When the largest aperture is open, expiration takes place without appreciable resistance As the disc is turned to progressively smaller openings, the patient exhales against a positive pressure equivalent to 1, 2, 3 or 4 cm of water, respectively. Certain of these masks utilize a water bottle and tubing instead of the pressure meter; here, the expiratory positive pressure is regulated by adjusting the depth of tubing below the surface of the water Both these devices are capable of supplying inspired air concentrations of oxygen from 40 to 95 per cent (depending on the meter setting and the oxygen flow) at expiratory pressures of 0 to 6 cm of water. The beneficial action of expiratory positive pressure breathing depends on elevation of pressure in the airways with an increase in intrathoracic and right atrial pressure with a decrease in venous return and cardiac output. The peripheral venous pressure rises, with some loss of fluid to the tissues, and a consequent reduction of blood volume. Thus, the effects of positive pressure respiration resemble those of tourniquets and venesection. Positive pressure breathing, however, raises lymphatic and cerebrospinal fluid pressures[1] and also probably increases the work of breathing. The recent report of Miller and Sproule[10] suggests that IPPB/I-O_2 therapy is superior to the expiratory positive pressure oxygen.

Face Tents

Loose-fitting oxygen masks or so-called face tents (Fig 2E) have been employed over the past 60 years in many forms, the latest having been introduced by Segal The face tent is constructed of a clear, flexible plastic substance, and fits comfortably over the lower portion of the patient's face. The top of the tent opens widely for an easy egress of exhaled gases and vapors Humidified oxygen enters the plastic shield through a shower-head dispersal system that eliminates much of the discomfort noted with nasal catheters and related apparatus Adequate visibility is ensured, and a sense of confinement, such as is often noted with prolonged use of mask therapy, is usually not noted

Open Box Tents

First introduced by Burgess and associates in 1932, head hoods with closed tops, or box tents with open tops, applied the principle that oxygen, which is heavier than air, will accumulate in high concentrations at the bottom of a container closed on all sides Such hoods (Fig. 4) are valuable in the therapy of children, and adults who do not tolerate nasal catheter technics They are commonly made of plastic, with an opening on one side to admit the patient's head, the top is either completely open, or opened and closed, to allow diffusion of carbon dioxide outward A cooling tray for ice is mounted on the inside above the patient's head. Alveolar oxygen concentrations of 40 per cent may be obtained when a 6 to 7 L flow of oxygen is provided, lower flow rates encourage the development of excessive concentrations of carbon dioxide, of the order of 2 to 3 per cent at times, in the system. The use of the injector

The disadvantages of oxygen tent therapy far outweigh the advantages, so that for adults the oxygen tent should be used only under unusual circumstances. The oxygen tent is the most inefficient of the methods of administering oxygen, with flow of 15 L. per minute yielding alveolar concentrations of only 40 to 45 per cent even with careful sealing of the canopy at all points If the canopy is opened frequently or improperly sealed, the O_2 concentration obtainable would be even less. Ordinarily, the O_2 tent has a low humidity which has a drying effect usually deleterious to the respiratory passages Although one of the "selling points" of the oxygen tent has been its function as an air conditioner, there is a distinct danger of needlessly chilling seriously ill patients, which may well occur in an oxygen tent. An oxygen tent complicates the nursing care greatly, and may result in some neglect of the patient because the nurses try to keep opening of the canopy to a minimum. The oxygen tent is the one method of oxygen administration in which there is a distinct fire hazard

With modern efficient and inexpensive air conditioners available, it seems unwise to use the oxygen tent merely for air-conditioning, since the nasal cannula and the new lightweight plastic masks are well tolerated and provide higher O_2 concentrations than can be achieved in an oxygen tent Finally the oxygen tent is quite costly initially and is the most expensive of all methods to operate It would appear, therefore, that for adults an oxygen tent should be used only if no other suitable means of O_2 administration is available or tolerated by the patient.

Portable Oxygen Devices

Various devices comprising portable oxygen tanks of different sizes may be employed, usually with mask administration, for short-term treatment of hypoxic patients Recently, Barach has described the use of two new types of oxygen equipment for ambulatory patients One of these is a two and three-quarter pound oxygen cylinder which contains about 180 L of oxygen under 1,800 pounds pressure.* This

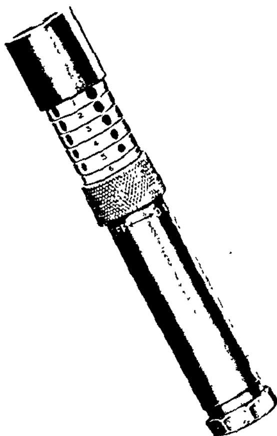


Fig 6—Oxy-Hale cigar-sized inhalation unit

cylinder, which is strapped over the shoulder or neck of the patient, hangs at the side with the regulator set at the desired flow A flow rate of 6 L per minute may permit a hypoxic patient to walk for one-half hour at a moderate rate without dyspnea. A flow rate of 4 L per minute may be sufficient to prevent breathlessness in most patients with chronic pulmonary emphysema during exertion, and 2 L per minute may provide these individuals with relief of breathlessness while at rest These lightweight cylinders may be refilled from larger high pressure cylinders when necessary

The second of these newer portable devices described by Barach is the cigar-sized "Oxy-Hale"* apparatus (Fig 6) which can hold a 3 L. oxygen cylinder under 5,000 pounds pressure, 3, 5 and 8 cylinders may be manifolded into the basic apparatus to provide from 9 to

* Supplied by Controlled Pressure, Inc, Erie, Pennsylvania

* Supplied by Controlled Pressure, Inc, Erie, Pennsylvania

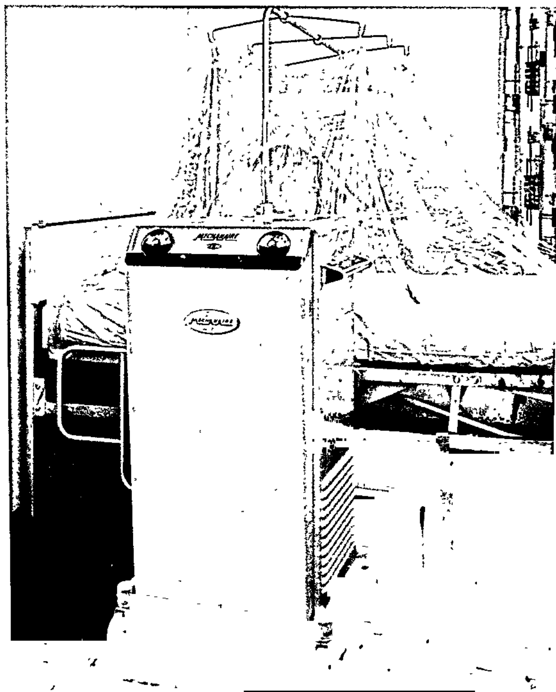


FIG 5—An example of the newer light-weight plastic oxygen tents providing comfort and perfect visibility for the patient

tents provide an automatic cut-off when the oxygen tension falls below a predetermined level, and a much higher oxygen flow to build up to the required concentration Tent temperatures must also be monitored carefully, maintaining a temperature from 65 to 80 degrees depending on the individual patient's comfort. It has been suggested that tent temperatures in very hot weather be set no more than 10 to 15 degrees below room temperature, so that opening the canopy does not expose the patient to a sudden temperature change with possible adverse effects Electrical connections and patency of the air ducts, evaporator coil grills and the coils themselves all should be checked at frequent intervals

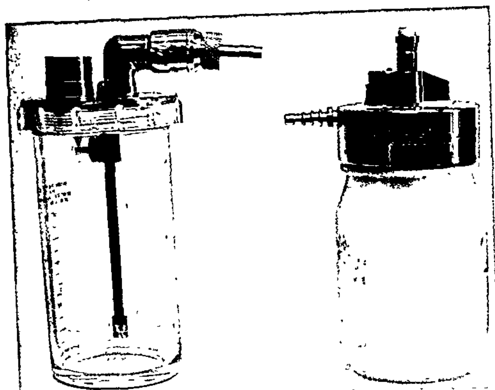


FIG 8—Humidifier and aerosol generator

ith sidevents are available for aerosol ther-
py in this situation and may also be used
or the application of expiratory positive pres-
ure. Humidification necessary may vary from
0 per cent relative humidity to saturation at
ear body temperature

In the management of prolonged respira-
ory distress, "Fog" therapy may be invalua-
ble. Using the older methods of humidification,
drops of moisture may settle out if there is a
sudden change of temperature or pressure
within an oxygen tent or incubator; these drop-
lets are too large for adequate penetration of
the tracheobronchial tree, and are therefore
unable to mix with, and dilute, secretions and
aid normal ciliary action "Fog" therapy is
carried out with an apparatus which mixes two
streams of air, one cold and the other heated
and supersaturated, using specially constructed
incubators or tents which permit rapid re-
circulation of air, removal of droplets by cool-
ing, rewarming and rehumidification. The re-
sulting fine moisture particles mix with, and
dilute, tracheobronchial mucous and aspirated
matter and facilitate normal ciliary action.
Special "Fog Rooms" combined with genera-
tors are used at some institutions in preference
to enclosing devices.

In recent years, aerosols have been used in
several ways in the treatment of broncho-
pulmonary disease. Aerosols are fine suspen-
sions of liquid particles in a gas, with a rela-
tively uniform particle size ranging from 0 5
to 3 0 microns Aerosols are administered with
nebulizers, which usually hold small volumes
(less than 5 cc. of liquid), or larger units
known as *aerosol generators* (FIG 8) which
contain up to 500 cc. The aerosol is produced
by a jet of compressed air or oxygen blown
through a narrow orifice and producing a Ven-
turi effect The solution is drawn up through
another tube placed at right angles to the first,
and then is broken up into fine particles which
are hurled against a baffle system, here, the
larger particles coalesce, leaving the smaller
ones for inhalation.

Segal has recently classified aerosols into
eight therapeutic categories: (1) anticholin-
ergics, (2) antimicrobials, (3) antihistamines,
(4) bronchodilators, (5) bronchovasoconstric-
tors, (6) detergolytics, (7) enzymes and (8)
miscellaneous, including humidifying sub-

24 L of pure oxygen A Venturi or mixing device and an adjustable sleeve attached to the cylinder case permit the pure oxygen in the 3 L cylinder to draw in 3 to 8 L of air, thus providing a larger volume of oxygen-enriched air for inspiration The various sleeve settings allow adjustment of oxygen concentrations from the lower percentages adequate in emphysematous patients to the 90 per cent or more required by patients with coronary artery disease and congestive heart failure The small size of the apparatus and cylinders makes this device ideal for the patient to carry in pocket, purse or briefcase. Studies by Segal with this apparatus indicate that one minute of therapy with 18 inhalations at a sleeve setting to provide 40 per cent oxygen, is capable of raising arterial oxygen saturation from a control value of 57.2 per cent to 93 per cent after one minute, with values remaining above the control levels at the end of 5 minutes.

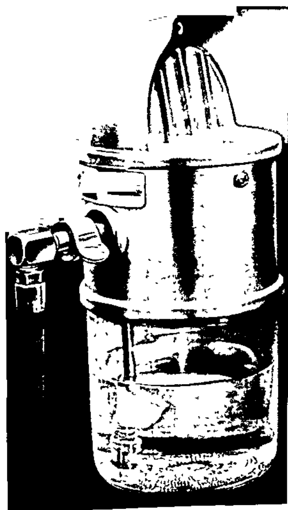


Fig 7.—Large aerosol generator for use in closed or open tents

Humidification and Aerosol Therapy

Atmospheric humidity is usually expressed in relative terms as a percentage of the absolute water vapor contained per unit of air at any given temperature and pressure. At higher temperatures, the atmosphere takes up more water vapor, while a process of "raining out" takes place at lower temperatures. Oxygen, as an almost dry gas, must be at least partially humidified on introduction into the upper airway, since expired air is fully saturated at a higher temperature, that of the body. Although oxygen and air mixtures may be completely saturated at room temperatures (about 25C.), these mixtures, when heated to body temperatures are relatively desaturated and require the addition of water vapor from the mucosa lining the tracheobronchial tree.

Normally, conditioning of the inhaled air by the addition of heat and humidity begins with the entrance of the air into the mouth and nasopharynx Disease states, dehydration, the exhibition of atropine and antihistaminic drugs and certain processes affecting both the quantity and consistency of secretions, all call for humidification of the inspired air or more effective similar procedures

With catheter or cannula therapy, humidification of the atmosphere is desirable for long-term management Recent observations indicate that bacterial contamination occurs frequently in the solutions of conventional humidifiers, presenting another source of hospital infection to patients receiving inhalation therapy The larger type of aerosol generator (Figs 7 and 8) which can be sterilized and refilled daily, may be preferable. Humidification may be omitted during short-term therapy using snug rubber masks, disposable plastic masks and open top face tents, because of the high humidity which occurs from the expired air entering the enclosed space; humidification is mandatory if treatment is prolonged

Major drying effects lead to accumulation of thick tenacious exudates in the trachea after most tracheostomies Special plastic collars

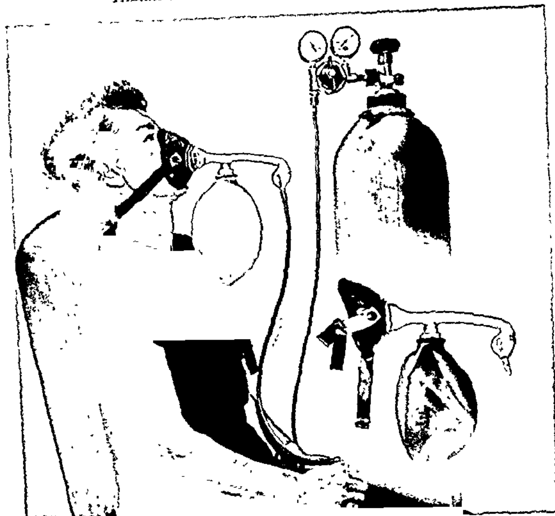


Fig 9—Apparatus for aerosol nebulization with rebreathing bag

and 11) raise the temperature of the liquid and air breathed by the patient to 105 to 125F, the heated air stream is at 100 per cent relative humidity and contains suspended water particles[6] Condensation of aerosol and water vapor takes place on the relatively colder surfaces of the respiratory passages. Aerosol solutions containing from 5 to 20 per cent propylene glycol inhibit evaporation of the suspended water particles still further, assuring precipitation of moisture on the mucosal surfaces Liquefaction of mucous is thereby facilitated The same apparatus may be employed, with a solution of 20 per cent propylene glycol and 80 per cent water, 10 to 15 per cent saline, as an aid in the expectoration of secretions for cytologic study. Individual treatments lasting 20 to 30 minutes are usually prescribed three or four times a day, often with preliminary bronchodilator "priming" Detergents (Alevaire, Tergemist) may be helpful for heated aerosol therapy

Intermittent Positive Pressure Breathing

The intermittent application of positive pressure to the upper airway during the inspiratory phase of the respiratory cycle has undoubtedly been the most popular of the mechanical devices which attempt to establish a pressure gradient from the mouth to the pleural space This is accomplished with a system connecting pressure-tight masks or mouthpieces worn by the patient with a flow or pressure-sensitive inspiratory demand valve which delivers compressed gases from storage cylinders or other external sources. The pa-

stances, alcohol, physiologic saline, bacterial stains Of these categories, the major therapeutic areas in which aerosols are used are: (a) bronchodilatation and (b) humidification, including liquefaction of bronchial secretions

Bronchodilator aerosols are used in those cases where appreciable bronchospasm is discovered either from history and physical findings or from responses to pulmonary function testing The most frequently employed bronchodilators are 1 100 racemic epinephrine *preparations (Vaponefrin and Solution A)*; *iso*propylarterenol (Isuprel) and Aerolone compound These are usually diluted to 2 or 3 ml with saline, water or one of the detergents The hand bulb powered nebulizer is the most widely used for this purpose but requires good co-ordination between the hand bulb squeezing and the inhalation More satisfactory nebulization, particularly for prolonged periods, is obtained by connecting a small motor compressor or O_2 tank to the nebulizer with a Y-tube incorporated in the system The Y-tube must be closed with the patient's thumb on inspiration, if expensive medication is not to be wasted The smaller "measured dose" units are less satisfactory, because particle size is rarely uniform and a vapor, rather than an aerosol, is usually produced Recently, the gas phase of dichlorodifluoromethane has been utilized as a safe and *efficacious propellant for the nebulization of* bronchodilator aerosols *

The patient should be instructed to place the nebulizer at the lips with the mouth open On inspiration, *both the aerosol and an air stream* are inhaled; holding the breath at the peak of inspiration for a moment allows deeper penetration of the aerosol Emphasis is placed on starting the nebulization after forced expiration—immediately before inspiration, since there is evidence indicating that the first portion of the gas inhaled may be preferentially directed to the more poorly ventilated areas Concentrated bronchodilators are used in nebulizers when only a few squeezes of the hand bulb and 6 to 8 inspiratory efforts are sufficient For longer treatments, using powered attachments (Fig. 9), 0 5 ml. of the bronchodilator agent is diluted with 1.0 to 3 0 ml. of the vehicle. Antibiotics and enzymes in appropriate concentrations may be added Each full treatment usually takes 10 to 20 minutes and is given 2 to 4 times daily.

The aerosol generators are utilized when continuous or intermittent therapy is prescribed Humidifying liquids, liquefying aerosols and other substances are inhaled through a mask, mouthpiece, face tent or open top tent *Alevaire, or other aerosols which contain glyc*erine or similar substances, must not be used in a closed oxygen tent, because deposition of the aerosol on the refrigeration coils may damage the motor

It is important to understand that humidification and the liquefying of bronchial secretions by aerosols has but one objective: increasing the amount of water vapor and micronized water particles in the tracheobronchial tree Detergents such as Alevaire and Tergemist help lower the surface tension and permit better ingress of water into the thick secretions To accomplish this purpose large (500 ml) aerosol generators are necessary and these should run at least 30 minutes out of every hour A frequent error is the attempt to achieve "humidification" by using a hand nebulizer with only 2 to 3 ml. of liquid *four times a day It is worthy of reiteration* to insist that large quantities of aerosol are necessary to achieve the proper humidification and liquefaction of secretions in patients with *bronchopulmonary disease The most con*venient way of administering these aerosols is via a pump or compressed air into a lightweight plastic mask which can easily be placed *over the patient's nose and mouth*

The recently introduced heated aerosol devices may be of great assistance in various bronchopulmonary diseases, and particularly in tracheobronchial irritation, *of both chemical* or infectious origin These thermostatically controlled super-heated nebulizers* (Figs. 10

* The gas phase of dichlorodifluoromethane is supplied in cartridges as Halon by Thomas J Mahon, Inc, Englewood Cliffs, N. J.

* O E M *Heated Nebulizer*, O E M Corporation, East Norwalk, Conn Super Heated Nebulizer with Quiet Aerosol Pump, Inhalational Equipment Co, Inc New York, 28, N Y Tepid Mist, Mist O2 Gen Equipment Co, Oakland, 7, Cal

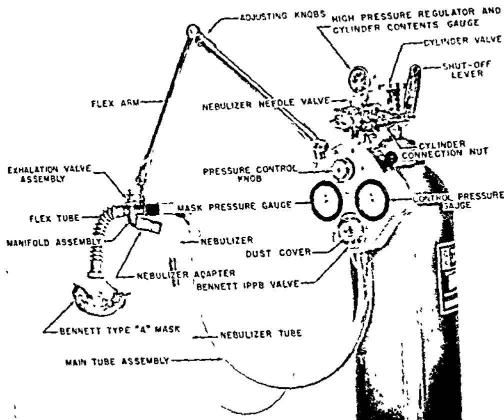


FIG 12—A modern IPPB/I unit

spiratory characteristics of the individual patient receiving treatment.

IPPB/I devices allow the lungs to be inflated actively to a greater degree than occurs with normal inspiration, enabling the patient to obtain a more adequate ventilation without increased breathing effort Fluoroscopic examination commonly discloses more efficient diaphragmatic excursions and improved aeration of the lung bases The bronchi widen and elongate during the inspiratory phase, and bronchial resistance decreases Improved bronchial drainage has been attributed to the development of a higher peak flow rate during expiration as compared with inspiration in patients receiving IPPB/I therapy. Segal,[11] while reporting decreased maximal breathing and vital capacity values in patients with bronchial asthma and pulmonary emphysema receiving IPPB/I alone, notes that this therapy in concert with bronchodilator aerosols leads to significant improvement in these measurements In normal subjects and patients with chronic pulmonary disease, the respiratory minute volume increases, usually as the result of a larger tidal volume In situations in which the alveoli are unequally ventilated and perfused, the distribution of the inspired air is improved, the alveoli are ventilated more uniformly, and the residual air volume is often reduced A higher arterial oxygen saturation results The temporary hyperventilation induced washes out the increased CO_2 present in many patients and corrects respiratory acidosis, thereby enabling the breathing center to regain its sensitivity to CO_2 stimulation. IPPB/I is thus a safer method of administering oxygen in the presence of respiratory acidosis than the conventional methods which, while reducing hypoxia, may depress respiration dangerously.

Segal and his associates[11] have delineated the hemodynamic effects of IPPB/I Normally, during the inspiratory phase of breathing the venous return to the right heart increases and right ventricular and pulmonary artery pressures fall, while the pulse pressure widens Right heart and pulse pressures diminish after

Fig 10—Heated nebulizer with pump as pressure source

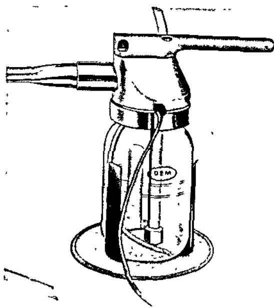


Fig 11—Portable heated aerosol generator

tient's own particular breathing pattern controls valve cycling; when the inspiratory pressure in the system reaches a preadjusted peak, the valve trips and the gas flow ceases Expiration then follows as a purely passive process produced by the elastic recoil of the lungs and chest cage, the next inspiration resumes the flow of gas through the valve, beginning another cycle

In the majority of machines available, flow principles are used which permit instantaneous flow rates large enough to satisfy even the most dyspneic patient. The most important characteristic of the particular mechanical valve used is its own flow resistance, which includes the opening pressure, and which determines the rate of flow of gas delivered for this certain pressure difference between line pressure and mask pressure. During the inspiratory phase, the pressure in the valve-mask system reaches a certain level and the mechanical valve closes, during expiration, gas flow from the lungs takes place against the resistance of the airway and the expiratory valve of the apparatus Therefore, the mask pressure curve obtained with a particular IPPB/I machine depends largely on the re-

models are now available for children with smaller dead space and more readily cycled at lower pressures In childhood asthma, IPPB/I may relieve and control symptoms and frequently reverse such changes as edema and bronchospasm. When combined with antimicrobial and/or mucolytic agents, this therapy provides active treatment of infection and atelectasis as well as prophylaxis against recurrence of these complications in mucoviscidosis Postoperatively, IPPB/I is helpful in preventing the pulmonary complications, particularly atelectasis, which may follow the use of cough-suppressing narcotics, tight dressings and prolonged immobilization. Further indications are in the treatment of depressed breathing due to alcohol, barbiturate or narcotic excesses, and in other emergencies involving inadequate respiration, such as the respiratory paralysis of poliomyelitis and other neurologic illnesses

There are at least six commercially available types of IPPB units which have varying degrees of advantage and disadvantage A variety of aerosols may be administered via a nebulizer attachment. Air, oxygen (100 per cent) or oxygen-helium (30 to 70 per cent) mixtures are satisfactory with a wide variety of tank and wall models and compressor units available.

In most instances, IPPB/I treatments should be given only by a trained person under the direction of the physician The patient's confidence may be obtained by discussing the apparatus and the goals of therapy in a straightforward and reassuring manner The patient should be reassured that the machine will not inflate them indefinitely but will shut off as soon as the pressure of inflation has reached its predetermined level Many patients tend to overventilate at first, so that mild tetany with carpopedal spasm may ensue, this may be prevented by instructing the patient to breathe deeply and slowly, allowing sufficient time for complete expiration Positive pressure will then take over the work of inspiration, and the valve will cycle with minimal effort The valve should be set for a low pressure during the first session, with progressive increases of the setting until a range of 15 to 20 cm. of water is finally reached Pressures should rarely exceed 12 to 15 cm. of water in patients with a history of spontaneous pneumothorax or mediastinal emphysema, or in the presence of giant air cysts

When IPPB/I is used for respiratory assistance or for humidification, it should be administered either continuously or at frequent intervals For chronic bronchopulmonary disease, treatments of 15 to 20 minutes' duration given 3 or 4 times daily should be continued as long as improvement continues In some instances, it may be advisable for the patient to have such an instrument in his home where he can use this as desired.

In those patients with severe bronchopulmonary disease who have thick tenacious bronchial secretions, IPPB/I is sometimes needed for respiratory assistance. In many instances it is wise to combine IPPB/I with a heated aerosol (to 125 F) in order to help liquefy

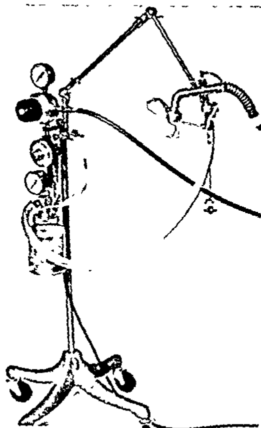


FIG 13—A heated aerosol generator attached to the main stream of an intermittent positive pressure device.

expiration begins The stroke volume of the right ventricle increases during inspiration and decreases during expiration Left ventricular stroke volume increases during expiration because there is an increased return of blood from the lungs Increased pulmonary artery flow during inspiration takes place despite a modest rise in pulmonary vascular resistance In patients with lung disease whose pulmonary vascular resistance is already high, a further rise in resistance during inspiration may not permit the increased venous return to develop a larger stroke volume, particularly if there is associated cardiac impairment

During the use of IPPB/I, the same sequence occurs, but in reverse fashion, the drop of right ventricular output during the rising mask pressure of inspiration may or may not be compensated when the mask pressure falls during exhalation Opposite events occur in the left heart, but with the qualification that the increased output during inspiration can be maintained for only three to five pulse beats by the displacement of blood from the lungs, if the inspiratory mask pressure is prolonged, the arterial pulse pressure drops following an initial rise Variations in right ventricular stroke volume are crucial in relation to these changes in cardiac output Right ventricular net filling pressure during IPPB/I decreases during periods of increased intrapleural pressure and increases during periods of falling intrapleural pressure If mask pressure returns to near-atmospheric pressure during the expiratory phase of the breathing cycle, the embarrassment imposed on a normal circulatory system is not of great importance When the circulating blood volume is normal, vascular tone adequate and reflex vasoconstriction possible, the peripheral pressure rises with the rise in pressure in the right auricle, capillary filtration is enhanced, and the water is lost to the tissues. If sympathetic pathways are ineffective, or if maximal reflex vasoconstriction has already occurred, the venous gradient may be abolished, leading to a drop in the venous return, cardiac output and arterial blood pressure

Side effects of IPPB/I may be produced by excessive pressure differences which can lead to overventilation with respiratory alkalosis and tetany Overdistention of the lung may be injurious depending on the time of treatment, as well as the pressure exerted; a high pressure exerted for a short time may be safer than a lower pressure applied for a longer period Any increase in intrathoracic pressure will be harmful to patients in shock, or if the venous return is already hampered. If positive pressure is transmitted along the gastrointestinal tract, the stomach and intestines may be distended, producing undesirable vagal reflexes, progressive difficulty in expanding the lungs and interference with the venous return Some observers have reported progressive right heart failure with peripheral edema

It should be emphasized that IPPB/I units are fundamentally respiratory assistors, and the primary indication for their use is the presence of a clinical state in which respiratory assistance is required In those postoperative patients who develop excessive secretions and poor air exchange, IPPB/I therapy can be most valuable Similarly, those desperate medical conditions in which the gas exchange is poor also will usually benefit from IPPB/I Thus, the contraindications to IPPB/I must always be relative, since the immediate need to achieve adequate respiratory exchange may overrule some of the usual contraindications

IPPB/I is usually contraindicated if there has been recent pulmonary bleeding, mediastinal emphysema or spontaneous pneumothorax, or in the treatment of patients under circulatory stress Congestive heart failure, unaccompanied by signs of circulatory collapse, may be responsive to this therapy

Favorable results with IPPB/I have been variously reported in the treatment of bronchospastic states, chronic bronchitis, bronchiectasis, diffuse obstructive emphysema, asthma, anthraco-silicosis, atelectasis, pulmonary fibrosis, pneumonia, pulmonary edema, and in the prevention or relief of CO_2 retention with respiratory acidosis It is of value in expansion of the unexpanded lungs and correction of partial atelectasis of newborns and in the oxygenation of anoxic infants in general, as indicated in Chapter 47 Special

rate which is similar to that of normal, vigorous natural cough. Such effects cannot be achieved with the use of IPPB/I therapy.

Inflation of the chest due to a gradual increase in pressure prevents development of high velocities which might blow the accumulated secretions deeper into the lungs. At peak inspiratory pressures, the bronchi are markedly widened, enabling air to traverse points of mucous plug obstruction and penetrate into the alveoli; this enhances the effect of the high expiratory volume flow rate and moves the secretions up and out. In patients with marked reduction of diaphragmatic excursions, the use of EWNP leads to greater diaphragmatic motion, better ventilation and improved drainage, particularly of the lower lobes of the lungs. The hyperventilation induced leads to a reduction in arterial P_{CO_2}, and an increase in pH and P_{O_2} in postoperative and emphysematous patients. Cardiovascular effects noted were those of positive-negative pressure devices in general, but the slight increase in venous pressure was below that seen with the use of tank respirators or IPPB/I machines. Minimal elevations of heart rate and blood pressure are usual, electrocardiographic alterations are limited to changes in electrical axis deviations such as are observed normally during deep inspiration and expiration Measurement of intragastric pressures, and thus indirectly of intra-abdominal pressures, showed that the mean peak pressures did not exceed 40 mm. Hg after EWNP, as contrasted with 90 mm Hg found during a vigorous natural cough These last data suggest that the patient treated with the Cofflator may experience less strain on a recent abdominal incision than would occur with spontaneous coughing

Patient co-operation is implicit if maximum benefit is to be derived from EWNP therapy The patient should be instructed to try to relax fully during the inspiratory phase, permitting the air volumes delivered to enter the lungs passively Expiration should also be passive, and the patient must refrain from attempting to exhale or cough during this phase of the breathing cycle. The effectiveness of EWNP may be heightened by preliminary administration of bronchodilator aerosols Treatment should be administered several times daily, each application of the Cofflator consisting of 5 or 6 intervals, each of 8 to 10 respiratory cycles

In comatose patients, in whom relaxation of the cardiac sphincter may occur, a gastric tube should be inserted prior to treatment to prevent overdistention of the stomach In poliomyelitis patients in the tank respirator, the foot of the respirator should be elevated to take advantage of the increased bronchial drainage of the head-down position Suction should be at hand, so that exsufflated material caught in the upper respiratory tract and mouth may be aspirated The tracheotomized patient can be treated by connecting the Cofflator to a cuffed tube inserted through the tracheotomy

Physical Therapy and Adjunctive Aids

Alterations predominantly on the expiratory side of the respiratory cycle characterize the physiologic defects of pulmonary emphysema and certain other chronic bronchopulmonary illnesses Trapping of air, prolongation of exhalation time and heightened muscular exertion and breathing work impose severe handicaps, to which an ineffective cough reflex is additive These abnormalities, if uncorrected or progressive, serve to perpetuate and intensify the underlying diffuse obstructive pathology. Purposeless, uncoordinated and inefficient patterns of respiratory muscle performance are commonly seen For these reasons, therapeutic exercises and adjunctive measures are being advocated in the over-all management of affected individuals Reviewing the mechanical and physiologic factors involved in such retraining programs, Sinclair postulates (1) Breathing exercises are not likely to alter the organic abnormalities of the lungs, (2) in order to minimize energy requirements of respiration, such exercises must eliminate non-contributory "associated" respiratory movements, (3) any deviation from the respiratory rate and tidal volume adopted by the individual patient should be introduced with proper caution, "since the level adopted naturally is probably associated with the minimal work of respiration"; (4) undue forceful

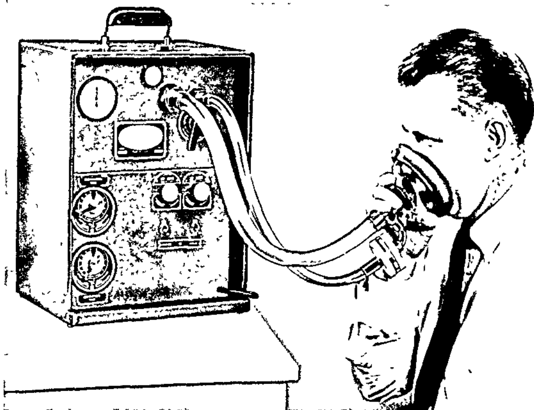


Fig 14—A "cough machine"—the Cofflator

secretions at the same time that respiratory assistance is being provided (Fig 13) In order to provide the maximal humidification, the aerosol generator must be in the mainstream of the air flow so as to provide more effective humidification of the gas breathed

Exsufflation with Negative Pressure

Inability to cough up mucous plugs or aspirate material is a frequent source of disability in a wide spectrum of conditions encountered in medical practice An ineffective cough reflex may be noted in respiratory depression accompanying the use of sedatives, narcotics and anesthetic agents, in intoxications and coma from all causes Impairment of the skeletal musculature due to nervous system disease, neuromuscular pathology, rib fractures, tight dressings and casts may have similar effects In a variety of chronic and acute bronchopulmonary diseases, there may be failure of the natural mechanisms for bronchial catharsis, and an effective cough will not occur because further expiratory collapse of the tracheobronchial tree results from excessive intrapleural-pulmonary pressure superimposed on an airway which is normally narrower on expiration, and further handicapped by mucous secretions, inflammatory swelling and bronchospasm Extensive studies by Barach and his associates[3] led to the development of mechanical measures leading to more adequate drainage of the respiratory passages utilizing Exsufflation with Negative Pressure (EWNP), or "the rapid blowing out of air from the lungs during the expiratory cycle"

The EWNP device (Cofflator*) consists of a high-speed blower motor unit which introduces into the lungs via a patient mask or mouthpiece a large volume of air (Fig 14) At the moment of peak inspiratory pressure, ranging from 20 to 40 mm Hg, a valve is automatically switched to the negative pressure side, producing a sharp drop in pressure which sweeps secretions and foreign matter toward the pharynx and mouth Length of inspiration and expiration are set at 1 5 to 2 5 seconds The rapid drop in pressure from 40 mm. Hg above atmosphere to 40 mm. Hg below, within 02 seconds time, produces an expiratory flow

* O E M Corporation, East Norwalk, Conn

exerts a pull on the diaphragm in the footward direction It is claimed that bronchial drainage and pulmonary circulation are likewise assisted by this therapy. A pneumatic vest fitted to the abdomen* can be synchronized with the use of IPPB/I so that rhythmic inflation of the vest during expiration aids diaphragmatic function and pulmonary emptying. Both inspiratory and expiratory sides of the respiratory cycle are thus patient controlled.

Further support of the ineffective diaphragmatic action may be attained with the fitting of an emphysema ("Gordon-Barach") belt† consisting of two spring metal bands attached to a pad placed below the navel; the lower band is the stronger and is designed to increase intra-abdominal pressure. Mechanical energy stored during the descent of the diaphragm aids the recoil of the lungs during expiration This support is available in various size ranges and may be adjusted to the bodily contours of thin patients by the addition of a soft upper band The belt should be worn from the time of arising until the hour of sleep, optimum use is attained by the forward-tilted position of the thorax

Lower chest expiratory support may be attempted by having the patient wrap his arms around the lower portion of the thorax, breathing out through pursed lips and sharply pulling the arms during expiration Mechanical assistance can be provided with the "Pneumatic Breathing Aid" (PBA) of Barach and Beck which consists of a lower thoracic vest and a flow-sensitive valve which is activated by expiratory flow Inspiration is accomplished by the patient's own respiratory drive; the lower thoracic vest is inflated by 40 mm Hg pressure during expiration and deflates rapidly at the end of this phase

In carefully chosen cases, therapeutic pneumoperitoneum may restore normal contour and position of the diaphragm so that improved function leads to emptying of hyperinflated alveoli, elimination of retained secretions and readjustment of the abnormal respiratory physiology. Whereas the emphysema belt provides similar assistance through the hours it is worn, pneumoperitoneum exerts its effects over the entire 24 hours of the day; furthermore, the compressible air allows easier inspiration Patients with relaxed abdominal muscles may require the use of the emphysema belt in conjunction with pneumoperitoneum. Pneumoperitoneum is most useful in those patients who cannot be taught abdominal and diaphragmatic breathing control, patients with excessive obstruction by accumulated secretions and the development of respiratory acidosis during infectious exacerbations of their disease, as well as individuals with abundant mucous accumulation and an inefficient cough reflex Introduction of small volumes of air (500 to 600 cc) intraperitoneally on frequent occasions is optimal; a larger amount may have undesirable effects, accentuating the abnormalities to be corrected. Simultaneous determination of the venous pressure may be useful in determining the possible help to be obtained from pneumoperitoneum, since Beck, Eastlake and Barach have observed either a drop or little change in venous pressure in patients who achieved excellent results, whereas a rise in venous pressure commonly foretold adverse results.

* "Exhalator", J. H. Emerson Company, Cambridge, 40, Mass.

† "Gordon-Barach Support", Spencer Inc, New Haven, 7, Conn

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exhalation may engender more airway resistance than it relieves, and (5) while the patient may learn a new breathing pattern, he cannot be taught true voluntary control of his diaphragms, nor more than a little of his chest wall

Miller, in a recent summary, has emphasized the need for "tailoring" therapy to the requirement of each person, taking into consideration his particular disease, the physiologic alterations present and their emotional setting, the patient's potential to understand and respond to training and the existence of sufficient rapport among doctor, patient and therapist to assure success Even the most enlightened subject is unable to comprehend or attempt the entire spectrum of corrective procedures at once, so that each measure must be introduced sequentially, allowing ample time for demonstration, practice and rest Evacuation of sputum, using forced coughing, postural drainage and EWNP, should be carried out before each session with the therapist, "priming" with bronchodilator, aerosols, particularly in conjunction with IPPB/I, is particularly valuable Preliminary instruction must be directed toward simple measures to encourage physical relaxation and to stretch the musculature of the shoulder girdle and upper chest wall. Correction of the postural defect of the childhood and young asthmatic should not be neglected, recent experience has indicated the value of group instruction during this phase of reconditioning

Barach has stressed the benefits of the 15 to 30 degree head-down position in this curriculum. Comfortable pillows should be placed beneath the head, and additional padding employed in the presence of skeletal deformity Fluoroscopic inspection of the motion of the diaphragm makes suitable positioning possible if the early treatments are carried out on the tilting x-ray table. Correct positioning is likewise facilitated with the help of angle-iron boards, elevation of the food end of the hospital (Gatch) bed, a hydraulic bed lifter,* or the convenient portable "head-down chair" and head-down table"* which are suitable for home use. An 8 to 15 pound sandbag placed over the upper abdomen will increase intra-abdominal pressure further and aid elevation of the diaphragm

With the patient properly positioned, and after instruction by the doctor or therapist, the subject is instructed to place one hand on the abdomen and lower ribs and the other on the chest wall, and to breathe so that the abdomen protrudes during inspiration and moves inward during expiration. Inspiration should be performed slowly through the nose and expiration through the nose or pursed lips After proficiency is achieved with these maneuvers, both the patient's hands should be placed below the navel, with the fingertips touching, so that the hands can be pressed fimly upward and inward during the terminal portion of expiration Both these exercises should be practiced for 15 to 20 minutes three or four *times daily*

Pursed-mouth breathing should be mandatory during the waking hours, and consists of a slow exhalation against the constricted lips This maneuver increases the pressure within the airways, diminishing the tendency for their early collapse and inducing air-flow through the smaller bronchi, contraction of the abdomial and expiratory musculature against this increased pressure results in elevation of the diaphragm, so that the over-all effect is a more satisfactory emptying of the lungs Barach has emphasized teaching the patient to lean forward when standing, walking or sitting up (The "Gorilla Walk"), because of the diminished ventilation with increase in total chest volume in this posture.

Diaphragmatic re-education may also be accomplished with the use of the Oscillating Bed † The effects of the head-down phase of the cycle duplicate those of the tilt-tables and chairs mentioned above, the foot-down phase

* Hydraulic bed lifters may be obtained from the Dupuy Company, Warsaw, Indiana, or the Zimmer Company, Warsaw, Indiana

* "Head-down Chair" and "Portable, Adjustable Head-down Table", O E M Corporation, East Norwalk, Connecticut

† "Oscillating Bed", J H Emerson Company, Cambridge, 40, Massachusetts

A Contribution to the Mechanism of Dyspnea, Based on the Response to Therapeutic Procedures

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THE purpose of this presentation is to evaluate the application of certain therapeutic procedures on dyspnea of cardiopulmonary origin. The response of the individual patient may illuminate our understanding of shortness of breath in a manner somewhat different from that achieved by measurements of respiratory function. For example, we have proposed the concept that reduction of pulmonary effort and the associated work of breathing, take precedence over the respiratory center in diffuse obstructive pulmonary emphysema; reduction of the pulmonary ventilation was observed to follow the application of a variety of physiologically directed procedures that enhanced the efficiency of alveolar ventilation, without reduction of the elevated arterial blood Pco_2, in short-term experiments.

Dyspnea refers to the sensation of difficult breathing, a subjective experience. In many, although not all instances, the physician may detect its presence by observation of labored breathing, or appraise the physiologic disturbance by laboratory tests. However, significant alteration of respiratory function from the normal may be discovered without the patient himself suffering from dyspnea, similarly, gross abnormalities in the structure of the lung are manifested by physical and other examination of the chest while the patient is breathing comfortably.

Chemical factors have been properly stressed as basic fundamental causes of shortness of breath. Although carbon dioxide, the primary stimulant of the respiratory center, regulates the ventilation of normal individuals in a precise way, its role in the maintenance of clinical dyspnea is far less clear. Thus, in cardiac insufficiency and uncomplicated bronchial asthma, this highly diffusible gas is not found in excess amounts in the blood unless the ventilation has been artificially depressed, as by excessive use of sedatives. In fact, in these clinical entities a decreased tension of CO_2 in the blood and alveolar air has been noted. In cases with pulmonary emphysema, the sensitivity of the respiratory center to CO_2 was *formerly thought to be* sufficiently impaired to reduce appreciably its stimulus to ventilation, but recent studies by Cherniak[4] and others have indicated that mechanical limitation of the chest bellows was responsible for the relatively decreased ventilatory reaction to inhalation of carbon dioxide. Our own clinical studies have revealed that lowering of the minute volume of *breathing has priority over chemical stimuli*; a homeostatic response functions in the direction of reducing the energy of breathing, as will be seen in the discussion which follows. Lack of oxygen, however, may be observed as an overt cause of dyspnea in the above-mentioned, as well as in other clinical syndromes, by the application of a properly conducted therapeutic test.

The difference between the response of the normal individual and the dyspneic patient is of considerable interest. Acute severe hypoxia may produce feelings of well-being and elation in the normal subject, followed, however, by unconsciousness and death without any sensation of difficult breathing. This response was first dramatically illustrated in the report of Tissandier during ascent of his balloon in the flight with Croce and Sivel in 1875.

> Body and mind become feebler. There is no suffering. On the contrary, one feels an inward joy. There is no thought of the dangerous position, one rises and is glad to be rising. I soon felt myself so weak that I could not even turn my head to look at my companions. I wished to call out that we were now 26,000

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exercises an effect which precipitates dyspnea in pulmonary emphysema, as well as in cardiac insufficiency, as a direct consequence of the increased ventilation and the increased work of breathing required to maintain the hypoxia-induced hyperventilation. In these instances, the augmented minute volume of breathing, undertaken at the expense of dyspnea, initiates a more efficient exchange of oxygen but to a much less extent carbon dioxide, which is also produced in larger amounts because of the increased work induced by hyperventilation That the physical effort of breathing is enhanced in pulmonary emphysema and pulmonary congestion was shown by the wide swings in intrapleural pressure between inspiration and expiration, found by Christie and Meakins in both of these clinical entities Although oxygen inhalation relieves both dyspnea and hypoxia, the elimination of CO_2 is instantly diminished by the lowered ventilation The manner in which adequate compensatory mechanisms may develop to excrete the carbon dioxide produced by the body has been discussed extensively by a number of contributors to a recent volume[3] Suffice it to say at this time that retention of CO_2 does not interfere with alleviation of dyspnea initiated by oxygen treatment, but rather imposes a special problem in the prevention of uncompensated respiratory acidosis, especially when administered without proper precautions, when controlled oxygen therapy is undertaken, the progressive rise in arterial and alveolar CO_2 makes possible a beneficent cycle in which carbon dioxide is eliminated at a higher concentration per liter of ventilation Thus, the homeostatic reaction permits the maintenance of a lowered minute volume of breathing, a lowered O_2 consumption and, consequently, a *lowered CO_2 production*

In patients with pulmonary fibrosis, in whom the arterial oxygen saturation may be similar to those of the group of cases of pulmonary emphysema which we have been discussing, inhalation of oxygen is not generally accompanied by a significant decrease in ventilation, nor a substantial relief of dyspnea, even though the arterial P_{O_2} is elevated as a result In this instance, as well as in other varieties of bronchopulmonary disease in which constriction of the respiratory passageway is present, including laryngeal and tracheal obstruction as well as chronic bronchitis of the smaller bronchi and bronchioles, the restricted ventilatory capacity results in a different kind of dyspnea It is not our present purpose to describe the physiologic disturbance from the standpoint of alterations in pulmonary function tests, but rather to gather information which will illuminate the mechanisms involved from the application of therapeutic procedures. Although inhalation of oxygen does indeed reduce *hypoxia* in these cases, the alleviation of dyspnea takes place primarily in those patients in whom the degree of oxygen want is severe, in whom pathologic changes have taken place in the pulmonary capillaries and alveoli

In purely obstructive lesions of the respiratory tract, an increase in the *effort* of breathing is experienced, interpreted by proprioceptive reflexes as the sensation of dyspnea In animals subjected to tracheal constriction, the intrapleural negative pressure is immediately increased at the end of inspiration and approaches more nearly to that of the atmosphere during expiration If air is inhaled under a positive pressure breathing system, e g, 6 cm H_2O above that of the atmosphere, the intrapleural inspiratory pressure is decreased in the direction of normal. A similar response takes place with the inhalation of helium-oxygen mixtures. When obstructive breathing is produced in human subjects by inducing them to breathe through a constricted orifice, the increased effort of breathing is experienced as dyspnea instantly, long before any alteration in the oxygen or CO_2 tension of the arterial blood takes place At the *onset* of an experiment of this kind, neither oxygen lack nor CO_2 retention are involved, and the chemical influence in the production of dyspnea does not exert itself until a later period, depending on the degree and duration of the study. Breathing under positive pressure or inhaling a helium-oxygen mixture is similarly helpful under these circumstances In fact, if a 90 per cent helium and 10 per cent oxygen atmosphere is breathed, the relief of dyspnea is striking for a very brief period, i.e., until the ventilatory stimulus of

feet, but my tongue was paralyzed All at once I shut my eyes and fell down powerless and lost all further memory

When the balloon descended from 28,820 feet of its own accord, Tissandier's two companions were dead

The response to hypoxia of similar severity is rather different in men acclimatized at high mountainous regions or in chambers with the pressure lowered to altitude equivalent to 20,000 to 25,000 feet. The pulmonary ventilation is indeed gradually increased, but normal subjects at rest may be comfortable without the sensation of dyspnea In a patient with metastatic cancer involving the lung, in whom the arterial oxygen saturation was 89 per cent, acclimatization to a simulated altitude of 18,000 feet was accomplished without dyspnea. This type of adaptation to long-continued lack of oxygen is also at times found in cyanotic patients with cardiopulmonary disease However, in these latter instances, slight exertion is generally productive of an exacerbation of dyspnea as well as an increasing want of oxygen.

A slight lowering of the concentration (or pressure) of oxygen in the atmosphere is followed by dyspnea, even at rest, in the majority of patients with moderately advanced or severe pulmonary emphysema An altitude between 3,000 to 5,000 feet, which is well tolerated by the normal individual, will frequently provoke difficult breathing in patients of this type Similarly, a slight encroachment on the capacity to transport oxygen from the alveoli to the blood induced by infection, bronchospasm or alveolar overdistention is also followed by dyspnea which can be related, in part at least, to the exacerbation of hypoxia.

A few investigators have minimized the role of oxygen lack in the dyspnea of such clinical entities as cardiac insufficiency and pulmonary emphysema, because the arterial oxygen saturation was found to be normal or nearly normal. In some of these instances, although not in all, the arterial puncture itself resulted in a sufficient degree of hyperventilation to elevate the arterial Po_2 to higher levels than would be present during a period of basal ventilation In any event, patients with chronic pulmonary emphysema are ordinarily exquisitely sensitive both to lowering and raising the oxygen tension of the inspired atmosphere in terms of the ventilatory response, irrespective of whether the arterial oxygen saturation is in a high range, i e., 93 to 97 per cent. The burdensome ventilation adopted by the patient does appear in these instances to result in a higher arterial Po_2 than would be present if a lower and more comfortable minute volume of breathing were adopted. The cause of the dyspnea in these patients may be additionally appraised in the light of their response to therapeutic procedures

Any abrupt increase in ventilation, provoked by mild hypoxia or other factors, may become (or represent) a relatively high proportion of the patient's own maximal minute ventilation, a circumstance suggested by Means and Richards and Cournand as frequently characteristic of cardiopulmonary dyspnea A diminution of pulmonary reserve is accompanied by an increase in the physical effort of breathing, due in large part to the use of muscles not normally employed in respiration—the so-called "accessory muscles of breathing"—including those of the shoulder girdle, the neck and the upper intercostals during the inspiratory phase, and the abdominal and expiratory intercostals during expiration

The inhalation of moderately increased oxygen concentrations in the atmosphere is usually followed by a prompt or gradual relief of dyspnea, even in cases in which the arterial saturation had been found normal or nearly normal This specific response is not to be considered as a manifestation of respiratory depression since, in well regulated oxygen therapy, the minute volume is not depressed below normal nor does oxygen ordinarily produce a hypoventilation syndrome unless administered in unduly high concentrations It is not my purpose to discuss hypoventilation or respiratory acidosis, either as an entity which occurs spontaneously as a result of the progress of the disease, depression of the breathing centers by sedatives or the inhalation of high oxygen atmospheres.

We are, however, especially concerned in our discussion to point out that *oxygen lack itself*

mospheric pressure and exhalation is made either against a restricted orifice or through a water bottle to provide back pressure during expiration When continuous pressure breathing was produced in the helmet-hood apparatus, a pressure of 4 to 6 cm. was observed to be beneficial in cases with failure of the left heart, including those in which coronary thrombosis had taken place Orthopneic patients were observed who were able to lie flat without dyspnea when breathing 40 per cent oxygen under a continuous pressure of 6 cm. Recently, the development of a more feasible method of supplying CPPB by mask has offered the opportunity of utilizing this technic of pressure breathing on a more widespread scale than was possible with earlier models of mask or mouthpiece CPPB. In accounting for the relief of dyspnea in these cases and in overt acute pulmonary edema, it is necessary to consider various factors: diminished pulmonary congestion, an increased diameter of the bronchial passageway, improved alveolar penetration of the inhaled atmosphere and, secondarily, a more efficient gas exchange within the lungs Although inhalation of oxygen is indicated to counteract hypoxia and to lower the pulmonary ventilation, the abovementioned factors in themselves reduce dyspnea

Acute left ventricular failure and pulmonary edema have indeed been successfully treated without oxygen, i e , with the inhalation of air under positive pressure. There is, in fact, one instance of a woman who had had recurrent attacks of acute left ventricular insufficiency, with frank pulmonary edema, which had been customarily controlled by expiratory pressure breathing administered with a pressure mask, in whom an attack once took place in a region in which immediate treatment with oxygen was not available In her case, the employment of pursed-lip breathing with the mouth tightly [illegible] previously experienced This patient had had hypertensive vascular disease with coronary sclerosis. A similar result was reported in two cases of edema following severe hemorrhage, associated with chronic pulmonary tuberculosis, in which expiratory pressure breathing was conducted through the narrow orifice of a cigarette holder.

It has been known for a long time that mountain climbers, lumber men in Canada and men who break rock in Italy spontaneously employ pursed-lip breathing in expiration during these various forms of severe exercise. Individuals who walk up three to four flights of stairs have also been known to purse their lips at the end of exertions as a method of controlling their dyspnea. It would appear that the physiologic consequences here, too, include a retarding effect on the entrance of an excessive amount of blood into the right heart, i.e., the prevention of acute pulmonary congestion. The relief of dyspnea appears to involve these factors recited above: reduction of pulmonary congestion, improved aeration of the alveoli through widened bronchi, a relative increase in intrabronchial and intra-alveolar pressure, more efficient gas exchange between the alveoli and the arterial blood and, as an ultimate effect, reduction in the minute volume of breathing.

Some years ago, I described the physiologic advantages of grunting and groaning as related apparently to the increased intrapulmonary pressure developed under these circumstances. The expiratory grunt in lobar pneumonia, which was once a characteristic clinical manifestation of lobar pneumonia before the days of antibiotic therapy, did indeed appear to serve the purpose of preventing an undue quantity of blood entering the lungs In two instances in which morphine was employed to alleviate the patient's distress and eliminate the expiratory grunt, the swift onset of acute pulmonary edema in a period of 10 minutes [illegible] breathing has been enhanced by the symptomatic benefit which follows its use in left ventricular failure Similar benefit at times results from the use of pressure breathing in pulmonary edema even in the presence of peripheral circulatory failure, especially when mechanical augmentation of the respiration is obtained

hypoxia takes place The more localized the constriction, the more will be the benefit obtained from inhalation of the helium-oxygen mixture However, pressure breathing is of consistent value in the relief of dyspnea, irrespective of the development of either linear or turbulent flow due to prolonged or localized obstruction respectively, its characteristic manifestation in an earlier study being reduction of the minute volume of breathing

In cases with chronic obstructive bronchitis, with or without pulmonary fibrosis, and in cases with uncomplicated bronchial asthma, the inhalation of 100 per cent oxygen as a test procedure may be followed by no relief of dyspnea, whereas breathing air under a continuous positive pressure of 6 cm H_2O may initiate a prompt alleviation of the sensation of difficult breathing This response is also frequently discerned in cases with pulmonary emphysema in which the obstructive element, although different in its pathologic characteristics, is nevertheless generally present Inflation of the lungs is aided by the positive (supra-atmospheric) pressure, which tends to force air into the lungs and to relieve the physical effort of the respiratory musculature During expiration, the presence of an enlarged bronchial passageway, induced by the 6 cm positive pressure, maintains the lumen of the bronchi in a more patent state than would be obtained if the pressure fell to that of the atmosphere, either in normal or in intermittent pressure breathing A more efficient exchange of oxygen and carbon dioxide is thereby accomplished, but the first noticeable relief of the subjective experience of labored breathing takes place as a consequence of the physical application of pressure, the reduction of the pulmonary ventilation and its resultant decrease in the effort of breathing, interpreted by proprioceptive reflexes. The increased contraction of the abdominal and lower intercostal expiratory musculature to eliminate air during the expiratory cycle is not, interestingly enough, felt as a conscious effort, provided the pressure during inspiration and expiration is maintained equal; the patient himself may not be aware of the use of his expiratory musculature in expelling air from his lungs, especially when continuous pressures of 4 to 5 cm. are used. It is only when the midposition of the lungs suddenly changes, as in breathing voluntarily at atmospheric pressure during the inspiratory cycle and exhaling against a positive pressure, that enhanced physical effort is perceived.

When an 80 per cent helium and 20 per cent oxygen mixture is inhaled in many of these cases with a proper apparatus, i e, one without resistance and without the application of a nose clamp and mouth piece, the sensation of relief may be experienced as soon as the lungs have been emptied of the retained nitrogen in the air atmosphere A mask in which the collecting bag is fully inflated (and comfortably applied) may be employed, although the helium-oxygen hood was previously found to be the most acceptable and effective method of utilizing this type of inhalational therapy, with and without pressure breathing

We have commented on some of the effects of pressure breathing in respect to the alleviation of obstructive dyspnea, in cases with bronchial asthma and pulmonary emphysema, the increase in the diameter of the smaller bronchi has been demonstrated, as well as the total increase in lung volume Another characteristic effect of pressure breathing is its tendency to decrease the volume of blood entering the right heart as a result of the increase in intrapulmonary pressure This physiologic effect, utilized in the treatment of left ventricular failure and acute pulmonary edema, is indeed among the most effective, if not both the most effective and feasible, method of achieving the therapeutic aim of reducing congestion of the lungs When the failing left ventricle is offered a smaller volume of blood, its tone may be increased, with a subsequent restoration of its ability to contract in a more efficient manner than previously Studies have also been made in which, even during the application of pressure breathing, the cardiac output has been found to be elevated toward the normal

Any form of supra-atmospheric pressure breathing may be employed to accomplish this purpose, including intermittent positive pressure breathing with the pressure sustained on the inspiratory side, expiratory pressure breathing, in which inspiration proceeds at at-

in the ventilatory equivalent of Anthony and Knipping—the amount of ventilation required per liter of oxygen consumption. In other cases, there was a marked decrease in the oxygen consumption, a reliable index of the decreased work of breathing Even though the vital capacity was reduced and the diameter of the bronchi as a whole decreased by the diminished lung volume, dyspnea was relieved It should be pointed out here that although bronchial diameter is lowered as a total response, it may well be that bronchiolar diameter of the better functioning parts of the lungs is increased, since the recoiling elastic pressure surrounding the walls of these smaller tubes is enhanced, thereby tending to prevent premature bronchial closure In any event, a reduction in the minute volume of breathing of 20 to 30 per cent unaccompanied by a lowering of the arterial oxygen saturation, retention of carbon dioxide or the development of a more acid pH points to a more efficient exchange of gases between the lungs and the blood, a response induced not only by better ventilation of the lower lobes of the lungs, which may or may not be involved in the emphysematous process, but by *increased ventilation of the alveoli at the hilum*, which invariably contains better preserved and better perfused lung parenchyma than overdistended areas at the periphery, which are apt to be relatively bloodless. This response illustrates the priority over the respiratory center of the factors that represent reduction of pulmonary effort and the associated energy of breathing In long-term use of the head-down position, or diaphragmatic breathing produced by any method, it would appear that some lowering of the arterial P_{CO_2} and elevation of the P_{O_2} would take place.

In a patient who had several weeks of training with the application of increasingly heavy buckshot bags on the abdomen, the reduction of pulmonary ventilation was accomplished by the application of 20 and 25 pounds to the midepigastrium when he was semirecumbent. The increased diaphragmatic excursion thus obtained, seen in Figure 1, resulted in lowering of the $\dot{V}_E$ from 6 3 to 4 7 and 4 0 L per minute respectively, with the O_2 removal rate increasing from 45 to 57 and 67 respectively. The fall in venous pressure from 68 to 62 represents an increased negativity of the intrapleural pressure which has previously been shown to be an accompaniment of elevation of the diaphragm, as induced by an emphysema belt or pneumoperitoneum.

The institution of diaphragmatic breathing is an example of redistribution of air, a selective ventilation indicating that the dyspnea of patients with pulmonary emphysema is not simply a matter of over-all compliance, impaired elasticity or hypoxia, but also a physiologically inefficient inflation of the periphery of the lungs, particularly the parenchyma near the upper thorax The relief of dyspnea produced by therapeutic elevation of the diaphragm is thus shown to be due to curtailment of the physical effort involved in employment of the accessory muscles of breathing, *a decrease in the volume of ventilation* and provision of a better chemical exchange of gases. Results of the head-down position were so striking that we were again stimulated to utilize more consistently those measures (such as a belt) which maintain the diaphragm in a higher position during standing and walking. Furthermore, encouragement has been given to the study of the value of posture, especially the employment of the bending forward posture, which itself increases the relaxation pressure of the lung by reducing the visceral downward pull.

Although the bending forward posture is accompanied by increased lung volume and,

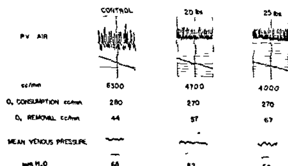


Fig. 1—Effect of increased diaphragmatic excursion on pulmonary ventilation and venous pressure induced by increments of weight on lower abdomen in emphysema

Much has been written about the stuporous or comatose states that have been precipitated by the treatment of patients with pulmonary emphysema with high concentrations of oxygen. However, in many patients suffering from chronic pulmonary as well as chronic cardiac insufficiency, a tendency toward increased sleep and mental relaxation has been observed without actual stupor, traceable not simply to CO_2 retention but to the relief of dyspnea itself In cases in which obstructive difficulties of breathing have been relieved with either pressure breathing or inhalation of helium-oxygen mixtures, or both, a similar onset of mental and physical relaxation has been, at times, observed The first patient with intractable asthma whom we treated with inhalation of an 80 per cent helium-20 per cent oxygen mixture lapsed into unconsciousness in approximately four minutes This unexpected response, alarming at the time, stimulated me to shake *him violently When awakened he remarked,* "This is the first natural sleep I have had in six weeks" Following a series of similar inhalations of helium with oxygen, a degree of bronchial relaxation took place that appeared to be related to the relief of dyspnea itself In subsequent studies on 54 cases, the effect of the decrease in the physical effort of breathing seemed to be cumulative, with a progressive decrease in the degree of bronchial constriction and the minute volume of breathing It is, of course, clear that certain central nervous system sedatives which relieve anxiety are at times followed not only by a decrease in ventilation, but by subsequent bronchial relaxation. Hyperventilation, beyond the metabolic requirement of the individual, leads to increased laryngobronchial spasm, coronary insufficiency and a train of symptoms due to alkalosis

The feeling of danger that the patient with difficult breathing so often experiences is itself an inducement to hyperventilation If the bronchial system is considered as a dynamic mechanism qualified to deliver a customary amount of air back and forth from the lung, then the movement of an excessive tidal volume will, of itself, produce increasing turbulence of flow; or, in other words, exercise an increasing constricting influence. This is na rally all the more significant in patients whom narrowing of the bronchi is already p ent, in whom it is almost as injurious to dou the ventilation as to reduce the bronc lumen itself. It is, therefore, of considera importance to utilize those methods availa to reduce the minute volume of breath without interfering with gas exchange. Am these methods is naturally included the re of anxiety, provided drugs which produce spiratory depression are not used to prom hypoventilation We have learned that hyp ventilation of nervous origin contributes to pathology of obstructive dyspnea as well as the sensation of dyspnea

Other therapeutic methods that enhance insight into the mechanism of dyspnea inclu procedures which improve the function of diaphragm This organ, long-acknowledged be a major part of the pulmonary bellows, m even in normal *individuals be to some exte* bypassed in favor of an excessive costal ty of breathing However, in patients with chron pulmonary disease, especially those with en physema in whom the physiopathology of t disease produces a special handicap in its el vation during the expiratory cycle, restoratio of even partial function to this organ general results in a significant relief of dyspnea Whe restored to its convex shape by pressure on i under surface, either through the weight buckshot bags applied to the abdomen or th use of a properly designed belt, the resultan contraction of the dome makes for a more e ficient type of ventilation, with decrease movement of the accessory muscles of breath ing, diminished physical effort and relief dyspnea Quantitative studies, carried out i patients in whom the thorax was tilted head ward at an angle between 15 and 22 degree *indicated that the pressure of the viscera uti* lized to elevate the diaphragm to a highe position in the chest reulted in a marked in crease in the efficiency of ventilation Gas ex change within the lungs was maintained even with a decisive fall in total pulmonary ventila tion, as revealed by measurement of the P_{O_2} P_{CO_2} and pH of arterial *blood There was,* in addition, a notable improvement (decrease)

which is well perfused with blood and anatomically better preserved than bullous areas at the periphery of the chest. It was also stated that the bronchiolar lumen may well be greater because of the added relaxation pressure of a less distended lung

An example of analysis of the mechanism of dyspnea on the basis of therapeutic tests was revealed in a man of 61 who had had a variable amount of dyspnea on exertion for three years. The diagnosis of moderately severe pulmonary emphysema had been made on the basis of respiratory function tests and clinical history X-ray of his lungs did show some slight increase in aeration of the lower lobes, but the diaphragms moved well. His arterial oxygen saturation had been found to vary between 96 and 97 per cent at rest, decreasing on exercise to 88 per cent and, during the inhalation of 13 per cent oxygen for five minutes, diminishing still further to 80 per cent. Before bronchodilator aerosol inhalation, his 0 5 second expiratory capacity was 1.40 L. or 38 per cent of his total vital capacity. His one second FEC was 1 90 L or 51 per cent of the TVC, 3 70 L. or 98 per cent of predicted normal No change was then noted after bronchodilator inhalation Functional residual capacity was 4 49 L, residual volume 2 85 L, with a total lung capacity of 7.13 L The ratio of residual volume to total lung capacity was 39 per cent, and the index of intrapulmonary gas distribution was 2 per cent. The residual volume was increased; however, the index of intrapulmonary mixing was only slightly increased above the normal (for this laboratory) of 1 5 per cent. He had been warned against flying at altitudes above 5,000 feet without inhaling oxygen at the same time

Three months later the patient was seen in our office The therapeutic test of exercising with and without oxygen did not reveal significant relief of dyspnea as a result of 10 L per minute of oxygen delivered through a nasal cannula Furthermore, inhalation of 100 per cent oxygen over a six minute period showed only a very slight decrease in pulmonary ventilation as compared to the measurement made breathing air, namely, from 8 20 L. to 7 60 L. per minute However, the reponse to inhaling 80 per cent helium with 20 per cent oxygen was an immediate sensation of ease of breathing.

The vital capacity, when performed with a gradual exhalation, was 3.40 L.—2 70 L. when the patient was instructed to blow out forcibly and rapidly. Ten minutes after the inhalation of a bronchodilator aerosol the fast expiration was 3 20 L. The predicted normal in his case was 3 70 L. On the following day a rapid expiration after a full inspiration was recorded on an especially designed fast-moving drum. In FIGURE 2 it will be seen that the volume of the first second of the expiration was 607 cc; whereas, when the patient breathed under a continuous pressure of 8 cm, 1,480 cc. were expelled during this period. It was also noted, as a result of CPPB (produced by a negative pressure of 8 cm. surrounding the body of the patient) that 715 cc. additional air was expelled when the bronchi were dilated by the physical procedure employed Inspection of the graph indicates also that the inspiratory flow of air was more quickly consummated, and that the total respiratory cycle was

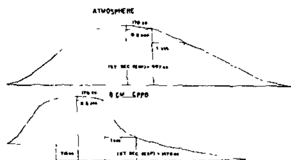


FIG 2—The results of continuous positive pressure breathing in a patient with chronic bronchial constriction, i e, chronic bronchitis and mild pulmonary emphysema indicated an increase in the volume and velocity of air delivered from the lungs in a rapid expiration, from 607 to 1,480 cc during the first second, after an expiratory pause of 0.8 seconds Pressure breathing, produced, in this instance, when the patient's body below the neck was subjected to a continuous negative pressure of 8 cm, was responsible for an increase in reserve air of 715 cc, an effect due to widening of the diameter of the smaller bronchi by CPPB Inspiration was more rapidly executed and the total respiratory cycle was shorter as a result of the physical effect of positive pressure in inspiration as well as expiration This response was achieved without the air of bronchodilator aerosols

therefore, increased dead space, the more efficient action of the diaphragm, plus the result that the bronchi are somewhat more patent and the fact that the mediastinum moves away from the posterior lobes of the lungs, compensates for the increased area over which gas must be diffused The relief obtained by patients who bend forward, either at a desk or in walking, is not consistently manifested by a lowering of the pulmonary ventilation unless a lower abdominal belt is worn at the same time The relief of dyspnea may not therefore always be traced to a lowering of the total minute volume of breathing, but cessation of use of the accessory muscles of breathing, to the better exchange of oxygen and carbon dioxide, and perhaps decrease in the total work of breathing The measurements we have made of the O_2 consumption in the bending forward position have been inconclusive Although it is not our intention to discuss alterations in tests of respiratory function, it is evident that any procedure which elevates the diaphragm must be followed by a development of a decreased functional residual air

The importance of oxygen lack in the dyspnea of effort in patients with pulmonary emphysema may be clearly visualized by having the patient carry on a prescribed exercise sufficient to provoke dyspnea while breathing an air atmosphere, and then contrast his subjective sensations with those perceived when a similar exercise is repeated during the inhalation of 8 L. per minute of oxygen through a plastic cannula or double-bent nasal tube The relief of the feeling of difficult breathing on exercise under these circumstances is not only evidence of the importance of the hypoxic factor, but is also utilized as a base line in a physical exercise, walking program with oxygen

The development of more practical methods of inhaling oxygen during walking has made it possible for us to extend the use of oxygen exercise programs which Cotes and Gibson[5] and our own group have found of such value in increasing cardiorespiratory reserve in patients with chronic respiratory and cardiorespiratory insufficiency. An exceptionally light-weight cylinder apparatus, weighing 3 pounds, supplies one-half hour of walking exercise at 6 L per minute; the pocket sized Oxy-Hale is used for two to six minutes, with the provision of 32 per cent oxygen during inspiration * With the use of these and similar equipment, it has become evident that respiratory depression does not occur when atmospheres containing between 32 and 50 per cent are inhaled while walking It is probable that almost all dyspneic pulmonary emphysema patients consume twice as much oxygen breathing oxygen as when breathing air, for several minutes after exertion [1, 8, 9]

The mechanisms by which dyspnea in pulmonary emphysema may be produced and relieved are so varied that quite opposite physiologically based procedures are at times helpful to the patient For example, positive pressure breathing has been shown to be of value as a result of enlargement of the bronchial and bronchiolar passageway However, expiratory negative pressure breathing has also been demonstrated to be of critical benefit in relieving dyspnea by producing a very high flow rate at the start of the expiratory cycle, as in exsufflation When the pressure gradient from the peripherally situated bronchi to the atmosphere is increased by the use of a mask negative pressure of 20 to 40 mm Hg or more, alveolar overdistention is diminished, dyspnea decreased and the vital capacity elevated. These two procedures—positive and negative pressure breathing—are often beneficial to the same type of pulmonary emphysema patient, but through the operation of entirely different mechanisms, as discussed above.

It is of interest to point out in this connection that although an increased lung volume is the basis for the widened diameter of the smaller noncartilaginous bronchi, which facilitates improved alveolar aeration and thereby decreases dyspnea, diaphragmatic elevation, which results in a decreased lung volume, is also responsible for relief of dyspnea, even though the over-all bronchial passageway is reduced because the efficiency of ventilation is greatly enhanced by selective distribution of air to the lung parenchyma near the hilum

* Supplied by Controlled Pressure Inc, Box 1933, Erie, Pa

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shorter A pneumotachygraphic record of the natural cough before and during CPPB revealed an increase from 5 8 to 6 8 L per second at the start of the expiratory cycle

The patient, on intradermal skin tests, revealed a high degree of skin reactions to a variety of inhalants Following the administration of a *compound containing aminophylline* and ephedrine, the productive cough of the patient almost entirely disappeared

We were now in a position to make a diagnosis of chronic bronchitis, probably chiefly of allergic origin, with a mild rather than a severe degree of pulmonary emphysema It was of interest, in this connection, that routine x-ray of the chest revealed a relatively narrow laryngeal and tracheal shadow The symptom of dyspnea seemed to us to be due in large part to a chronic bronchitis characterized by bronchospasm and allergic swelling of the walls of the small bronchi rather than impairment of pulmonary elasticity

In bullous (emphysematous) disease of the lung, the air oxygen ventilatory difference consistently reveals a substantial decrease in ventilation during the inhalation of oxygen Furthermore, exercise during oxygen inhalation is equally consistently followed by a sensation of relief Our belief that bronchial constriction was the more important factor producing this patient's dyspnea on moderate exertion was *substantiated by his experience during flights* made in an airplane at 11,000 feet Although the oxygen tension of the atmosphere was lowered, the density of the air was diminished, the patient at this altitude breathed without difficulty Although pulmonary ventilation was undoubtedly increased by hypoxia, the movement of air was apparently facilitated through those areas of the respiratory passageway in which turbulence took place

The application of therapeutics to enhance our understanding of dyspnea might be projected to a far greater extent than we have attempted. No reference has been made to antibiotics and chemotherapy, corticosteroid treatment, the administration of bronchodilator and bronchovasoconstricting solutions, the facilitation of bronchial drainage, exsufflation with negative pressure, respiratory acidosis, psychotherapy and a number of other measures which could rationally be included in a complete discussion of dyspnea as effected by treatment. We have attempted simply to illustrate some of the mechanisms involved in the production of dyspnea in which the application of physiologically based therapeutic *procedures has added to our understanding of* the mechanism itself

It may be emphasized that the patient himself has suggested to us the virtue of pressure breathing by his own use of pursed lip breathing, the value of diaphragmatic breathing by bending forward and squatting and, in addition, his preference for reduction of the pulmonary ventilation when provided with measures that enhance alveolar ventilation The studies in our clinic, old and recent, do not support routine, mechanically induced hyperventilation as a treatment for the conscious emphysematous patient with compensated carbon dioxide "acidosis," i e, increased P_{CO_2} with normal pH It has become increasingly clear that rehabilitation of these cases must be based on exercise of the breathing musculature and the body as a whole Buckshot bags, from 10 to 30 pounds, applied to the abdomen to develop the diaphragmatic muscle, spring-type emphysema belts, posture, walking during the inhalation of oxygen preceded by hand bulb nebulization of bronchodilators —*these measures should be part of* a regimen designed to restore respiratory and cardiorespiratory reserve, and to place the emphasis on the patient's own efforts to rehabilitate himself

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Section XI

DISEASES OF THE MEDIASTINUM

Section XI

DISEASES OF THE MEDIASTINUM

Physiologic Aspects of Esophageal Disease

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INASMUCH as the esophagus lies within the confines of the thorax, it is only natural that the chest physician should assume an interest in this organ, certainly to the same extent that he is concerned with the problems of the heart Esophageal disease often produces symptoms which are similar to those of pulmonary and cardiac problems Furthermore, esophageal obstruction may give rise to serious pulmonary complications, especially those associated with the aspiration of esophageal content Enlargements of the esophagus often must be considered in the differential diagnosis of mediastinal and pulmonary neoplasms, as well as abnormalities of the heart and great vessels within the thorax Certainly it is imperative that the specialist in thoracic disease be familiar with the esophagus and its diseases

This volume is primarily concerned with the physiologic aspects of thoracic problems Therefore, this chapter will be devoted largely to disturbances of function of the esophagus and their sequelae Organic obstructions will be considered only when they represent the end result of physiologic disturbances or when they must be considered in differential diagnosis.

Anatomic Considerations

The esophagus is a tube that passes through the thorax from the hypopharynx to the stomach and, in the normal adult, is about 25 cm in length The esophagus is lined by squamous cell epithelium, and the remainder of the mucosal layer consists of lamina propria and a rather prominent muscularis mucosae Outside of the submucosa are the two muscle layers, an inner circular and an outer longitudinal one. The adventitia is almost nonexistent, an unfortunate circumstance for the endoscopist who has produced a "split" in the course of instrumentation The muscularis propria is composed of striated muscle in the upper portion of the esophagus and smooth muscle in the distal segment. Between the circular and longitudinal layers of muscle lies the myenteric plexus of Auerbach Changes in this plexus are believed to be responsible for the disorder in achalasia

Sphincters are present at both the upper and lower limits of the esophagus The upper or pharyngo-esophageal sphincter is derived from the cricopharyngeus muscle and is well developed The lower or so-called cardiac sphincter is so poorly defined that its existence as an anatomic entity often has been denied On the other hand, Lerche[8] has offered a rather complicated anatomic description of the cardia wherein he describes areas of constriction which separate the terminal part into an ampulla and a gastroesophageal vestibule. There is, however, undeniable physiologic evidence of a sphincter at the lower end of the esophagus

Physiology of the Esophagus

The greatest amount of information concerning the physiology of the esophagus has been obtained from the study of pressures both within the esophagus and at its sphincters For many years, the swallowed balloon was used for investigative purposes, but such balloons had the disadvantage of stimulating the esoph-

agus to activity. In recent years, methods employed for investigation more accurately depict the behavior of the esophagus The comments in this section are based on investigative work carried out at the Mayo Clinic during the past 8 years.[2] However, it must be emphasized that many important contributions have been made by other investigators in this field and also by radiologists who have studied the esophagus in health and disease.

We measure intraluminal pressures with the aid of tiny electromagnetic pressure transducers (Fig 1). When single records are made, the transducer itself is passed into the esophagus However, when simultaneous records of pressure at different levels are desired, water-filled tubes (Fig 2) are swallowed by the subject or patient, and these tubes are connected to transducers situated outside the mouth of the individual As a rule, three simultaneous records are made with open portions of the tubes located at intervals of 5 cm. The output of the transducer is amplified and recorded with the aid of a photokymographic system. Measurements of pressure are made within the esophagus, at its sphincters and in the hypopharynx and stomach The intraluminal pressures are recorded both in the resting state and during and after deglutition While the intraluminal pressures are being measured, a pneumograph records respiratory movements, and a myograph indicates the initiation of the act of swallowing Respiratory movements produce a major deflection of the resting pressure recorded by the transducer. When the unit is in the abdomen, the respiratory deflection is upward or positive with inspiration; when it is in the thorax the pressure with inspiration is negative Thus, if the pressure-recording device is passed into the stomach and gradually withdrawn, the respiratory deflection will reverse itself as the unit leaves the abdomen and enters the thorax Thus, it is possible to tell exactly when the unit passes through the hiatus of the diaphragm This observation often is of considerable importance, especially with respect to the localization of the gastroesophageal junction

In the normal individual, both superior and inferior sphincters are closed except during the act of swallowing Fyke and Code[4] showed elevation of pressure in the resting state at both the upper and lower sphincters (Fig 3). However, both sphincters open when swallowing is initiated While the pharyngo-esophageal junction relaxes, the pharynx contracts (Fig 4) and the elevated resting pressure in the upper sphincter is abolished. The pharyngeal contraction then passes through the sphincter into the esophagus and becomes a peristaltic wave.

In the resting state the pressure within the esophagus is subatmospheric (Fig. 5). Meas-



Fig 1—The miniature electromagnetic pressure transducer. (Reprinted through courtesy of the publisher[2])

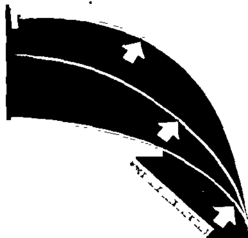


Fig 2—Three polyethylene tubes joined together for passage into esophagus and notched at intervals of 5 cm (Reprinted through courtesy of the publisher[10, 11])

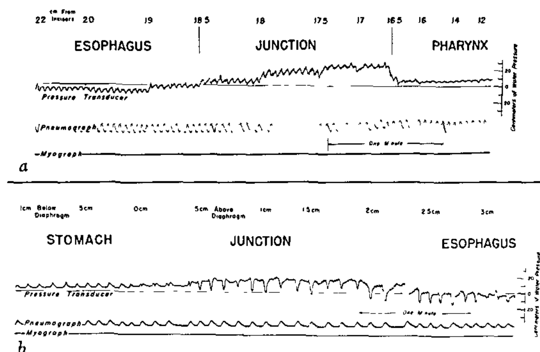


FIG 3—Normal resting pressures at the sphincters. (*A*) Pharyngo-esophageal junction; withdrawal of pressure transducer from esophagus to pharynx (*B*) Esophagogastric junction, withdrawal of transducer from stomach to esophagus (Reprinted through courtesy of the publisher[11])

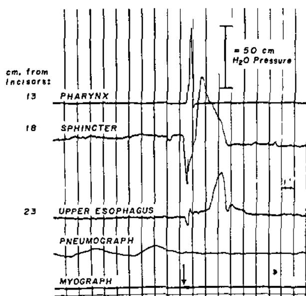


FIG 4—Deglutition pressures at the pharyngo- ... de- fol- ... nted through courtesy of the publisher[2])

urements of pressure in the esophagus at various levels after swallowing show that an orderly peristaltic contraction passes down to the distal esophagus in about 9 seconds (FIG. 6).

The pressure at the gastro-esophageal junction during rest is elevated not only above esophageal pressure but also above the pressure in the stomach Were it not for the elevated pressure at this junction, gastric secretion would flow into the esophagus, inasmuch as pressures within the abdomen are higher than those in the thorax The band of elevated pressure is about 2 5 cm long, and nearly half of this band is below the esophageal hiatus of the diaphragm and, therefore, within the abdomen

Studies of pressure made simultaneously in the lower part of the esophagus and the sphincter show that the pressure falls at the gastro-esophageal junction about 2 or 3 seconds after swallowing is initiated (FIG 7). The pressure in the sphincter rises as the peristaltic wave passes into it from the esophagus

Thus, the esophagus is a tube closed at both ends by sphincters Both sphincters open as a result of a swallowing effort. Except for organic obstructions of the esophagus, most of the causes of dysphagia are related to the failure of these sphincters to open. Our esophageal problems, therefore, will be divided into those

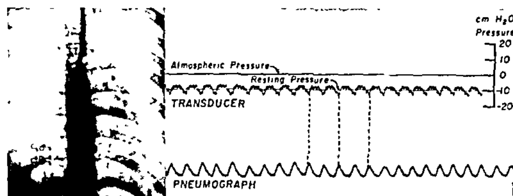


Fig 5—Pressure detector situated in the middle portion of the esophagus indicates normal pressure in the resting state Esophageal pressure decreased during inspiration (upward deflection of pneumograph) and increased with expiration (Reprinted through courtesy of the publisher[11])

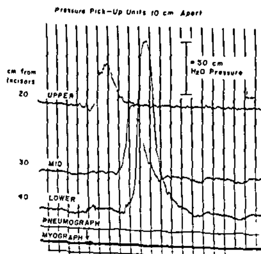


Fig 6—Normal deglutitory pressure sequence in upper, middle and lower parts of the esophagus

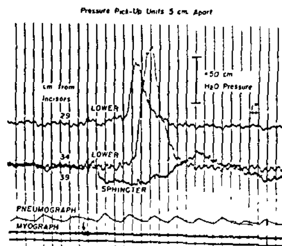


Fig 7—Simultaneous recordings of pressure in the lower part of the esophagus (upper two tracings) and in the gastroesophageal junctional sphincter (lower tracing) during deglutition. (Reprinted from Fyke, F E, Code, C F, and Schlegel, J F.: The gastroesophageal sphincter of human beings Gastroenterologia 86:135–150, 1956.)

of the upper and the lower part of the esophagus

Dysphagia in the Upper Part of the Esophagus

Bulbar Palsy and Muscular Disorders

Lesions of the brain stem frequently cause paralysis of the muscles of the throat. Weakness of the mylohyoid and pharyngeal constrictor muscles makes it difficult to initiate the act of swallowing. Cerebrovascular accidents, poliomyelitis, brain tumors (especially those of the cerebellopontine angle), injuries, unconscious states, myasthenia gravis, amyotrophic lateral sclerosis, dermatomyositis and others may produce serious problems in swallowing. Aspiration of food into the trachea and bronchial tree may ensue with all of the resulting pulmonary problems.

Patients with this type of problem often have more trouble with liquids than solids Often, they regurgitate fluid or food through the nose. They complain of choking and frequently have a chronic cough. Inspection of the pharynx and hypopharynx often discloses asymmetry and muscle weakness, and mucus tends to pool near the esophageal introitus and in the pyriform sinuses.

The treatment of dysphagia related to central nervous system or muscular disease is difficult. Obviously, the primary disease should be treated if possible. Otherwise, an indwelling nasogastric tube or repeated gavage feedings may be the only solution. Gastrostomy and tracheotomy are sometimes employed for the seriously ill patient.

Functional Dysphagia

The patient who fears that he will choke on his food usually can be classified as having functional dysphagia. This person eats slowly and chews his food endlessly, usually with his front teeth rather than with the molars. Persons with this syndrome have been called "rabbit chewers." They are unable to swallow pills and often avoid meats and many other solid foods. Whereas most people chew and swallow automatically with no conscious effort, the process is deliberate and forced in the patient with functional dysphagia. In some of the individuals, the process of swallowing is actually painful, probably because it is so artificial.

Normal deglutition is a complicated process requiring the co-ordination of many muscles. When the process is no longer reflexive and automatic, it is perhaps not surprising that the upper sphincter of the esophagus does not open readily. It seems likely that most cases of "cricospasm" are instances of functional dysphagia or poorly co-ordinated deglutition.

Plummer-Vinson Syndrome

Although Paterson[14] is credited with having first described this syndrome in the literature, it is perhaps better known as the Plummer-Vinson syndrome. The condition occurs almost exclusively in women, past the age of 40 years, with hypochromic anemia, false teeth, a smooth, shiny tongue, ulcerations at the corners of the mouth and other signs of vitamin deficiency. About a third have a palpable spleen and many have achlorhydria. All complain of dysphagia referred to the esophageal introitus. In a considerable number, esophagoscopy will demonstrate an esophageal web just below the esophageal introitus.

Unquestionably, the syndrome is attributable to vitamin deficiency. However, there has been much debate as to whether the deficiency is caused by poverty and starvation, by poor selection of food or by an hysterical fear of choking on food. In any case, a pharyngo-esophagitis is present, and in some instances cicatricial changes have taken place in the upper part of the esophagus. Carcinoma of the upper part of the esophagus, or hypopharyngeal and postericoid areas occurs rather commonly, according to Swedish authorities.[1] The relationship of cancer and the Plummer-Vinson syndrome may account for the relatively high incidence of upper esophageal carcinoma in women.

The treatment of the Plummer-Vinson syndrome has been successful to a considerable degree. Bougies may be passed over a previously swallowed thread, or dilatation may be effected by esophagoscopy. Subsequently, the patient must be reassured and encouraged to eat a normal diet. Often, the first swallowing of solid foods must be done in the presence of the physician. Specific treatment of the anemia and vitamin deficiency may be helpful.

Much remains to be learned about the etiology, pathogenesis and the exact nature of the physiologic disturbance in the various syndromes affecting the upper part of the esophagus. A great deal of physiologic evidence, however, backs up our current concepts regarding the disorders of the lower part of the esophagus and cardia.

Disorders of the Lower Part of the Esophagus

Achalasia

This condition has been described under a variety of synonyms including cardiospasm, mega-esophagus, preventriculosis and esophagectasia. The disease usually comes on rather insidiously. Symptoms may be intermittent at first but later become constant and progressive. The patient describes obstruction to swallowing localized low in the substernal area. This is often provoked by the ingestion of cold foods and may be just as bad or worse with liquids as with solid foods. Pain is not a common manifestation of achalasia, but it may be a feature in the early stages of the disorder. As



FIG 8—Roentgenographic appearance of achalasia (A) Moderate dilatation of esophagus (B) Diffuse dilatation of esophagus (C) Marked enlargement with elongation of esophagus (Reprinted from OLSEN, A M, HOLMAN, C B, AND ANDERSEN, H A The diagnosis of cardiospasm Dis Chest 23 477 [May] 1953)

the condition progresses, regurgitation is a constant feature

Roentgenographic evidence shows progressive dilatation of the esophagus and, ultimately, elongation and sacculation (FIG 8). Esophagoscopic examination is not too helpful because of the large amount of retained secretion in the esophagus. Esophagoscopy, however, should be performed on any patient when carcinoma is a possibility Carcinoma of the cardiac end of the stomach is more likely to simulate achalasia and is much more difficult to recognize by endoscopic means than carcinoma of the esophagus. Suitable biopsies are often difficult to obtain in gastric carcinoma, but cytologic diagnosis of material obtained by smear technic may be very useful. Likewise, the passage of a bougie over a previously swallowed thread may be a valuable diagnostic aid

Studies of esophageal motility have been of great value in the understanding, as well as the diagnosis, of achalasia In the resting state pressures are normal at both upper and lower sphincters. In contrast, the resting pressure within the esophagus usually equals the atmospheric pressure, probably because of retained food within the viscus In response to deglutition, the upper sphincter behaves normally. However, within the esophagus, pressure studies show complete absence of peristaltic activity. Feeble nonpropulsive contractions may occur simultaneously throughout the esophagus in achalasia (FIG 9).

At the esophagogastric junction, there is no wave of relaxation in response to the swallowing effort in achalasia, but the pressure at the gastroesophageal junction rises after swallowing This rise in pressure, although it occurs earlier than in health, is usually no greater in duration and amplitude than the increase of pressure observed at the end of the peristaltic sequence in normal individuals.

The subcutaneous injection of methacholine chloride (mecholyl) produces a distinct and prolonged elevation of pressure within the esophagus of most patients with achalasia (FIG 10) Since no such response occurs to this drug in other diseases or in health, the "mecholyl test" has considerable diagnostic significance Kramer and Ingelfinger[6] described

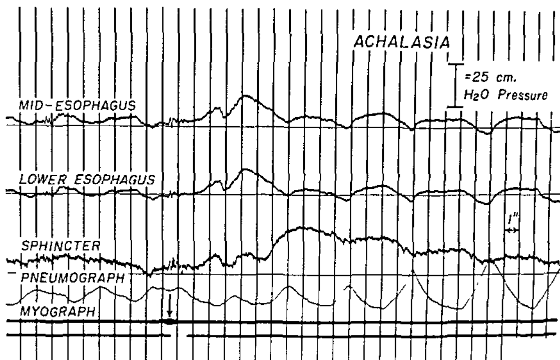


FIG 9.—Deglutition pressures in the esophagus and at the gastroesophageal sphincter of a patient with achalasia (Reprinted through courtesy of the publisher[2])

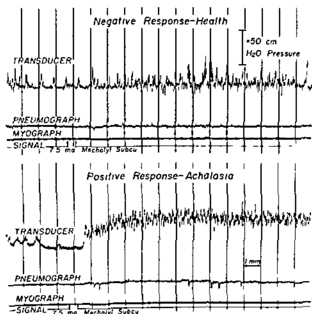


FIG 10—The methacholine hydrochloride (mecholyl) test in health and in achalasia (Reprinted through courtesy of the publisher.[2])

the mecholyl phenomenon in achalasia, and they expressed the view that this sensitivity to a parasympathomimetic agent was in keeping with Cannon's law of denervation.

Histologic studies of the esophageal wall in achalasia have revealed degeneration in the ganglion cells of Auerbach's plexus[7] Roentgenologic observations have lent support to the concept that the principal problem in achalasia is a disturbance of motility The physiologic measurement of intraluminal pressures has demonstrated two motor derangements in this disease the first is complete loss of peristalsis throughout the esophagus, and the second is failure of the lower sphincter to relax with swallowing Thus, although the term "achalasia," from the Greek word meaning no relaxation, more accurately describes the condition than *cardiospasm*, it does not specify the failure of peristalsis in the esophagus

Truly, physiologic treatment of achalasia would require the restoration of Auerbach's plexus With an intact nervous system we could anticipate renewed peristalsis and likewise that the wave of relaxation at the *gastroesophageal junction* would reappear in response to swallowing Unfortunately, re-establishment of the nerve supply to the esophageal musculature is not possible and, therefore, less physiologic means must be employed to treat the disease.

Methods of treating achalasia are directed

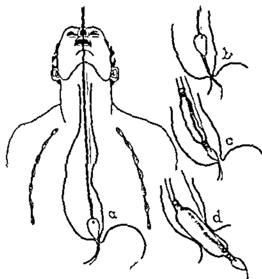


Fig 11—Treatment of achalasia by dilatation *a.* Passage of 41 F. olive-tipped bougie into stomach. *b.* A 50-F sound is passed into the stomach guided by a wire spiral *c* A hydrostatic dilator is passed to the cardia *d* Distention of the hydrostatic dilator across cardia (Reprinted from Olsen, A. M, Ellis, F. H, Jr, and Creamer, B · Cardiospasm [achalasia of the cardia] Am J Surg 93 299–307 [Feb] 1957)

toward reducing the pressure at the gastroesophageal junction and thereby weakening the lower sphincter. This may be accomplished by forceful dilatation of the sphincter or by surgical myotomy. In our hands, a suitable method of stretching the sphincter involves the use of a hydrostatic dilator passed over a previously swallowed thread (Fig. 11).[12] About 60 per cent of patients obtained permanent relief after a single effective dilatation, and an additional 20 per cent have obtained prolonged relief by repetition of the dilatation two or more times. In the remaining 20 per cent, relief of dysphagia, if any, is temporary.

The surgical treatment almost universally employed for achalasia is a modification of the procedure described by Heller (Fig. 12). An esophagomyotomy is performed without incising the mucosa of the esophagus or stomach. In our experience, the results of this procedure have been excellent or good in 85 per cent of the patients treated.[3]

Studies of pressures at the gastroesophageal

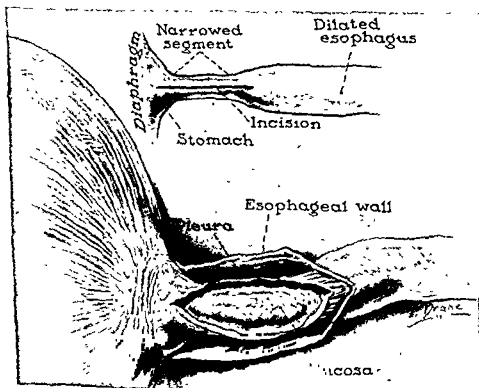


Fig 12.—Esoph...
Ellis, F. H.,
307 [Feb.] 195

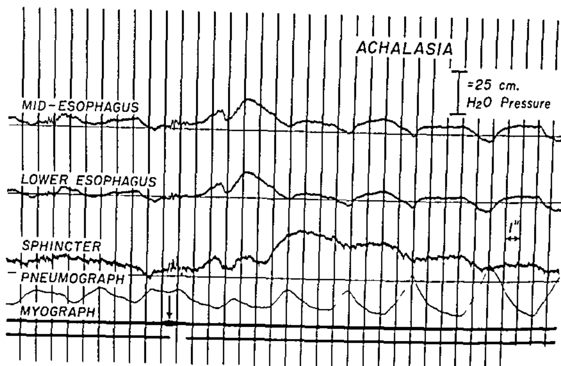


FIG 9—Deglutition pressures in the esophagus and at the gastroesophageal sphincter of a patient with achalasia (Reprinted through courtesy of the publisher[8])

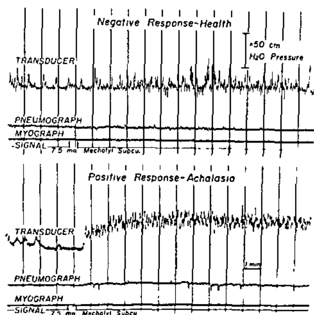


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Methods of treating achalasia are directed

hernia, duodenal ulcer, gallbladder disease and pancreatitis.

The roentgenologic appearance of diffuse spasm varies considerably, as indicated by the variety of synonyms for the condition (FIG. 13). In general, there is a spastic contraction, either diffuse or segmental, of the lower part of the esophagus Johnstone[5] demonstrated roentgenographically a thickening of the wall of the esophagus. Surgeons also have observed this phenomenon Many patients with diffuse spasm, however, give no evidence of any abnormality in the roentgenogram.

Esophageal motility studies have been invaluable in the recognition of patients with diffuse spasm[11] (FIG 14). In the resting state, pressures in the upper part of the esophagus and the body of the esophagus are normal. At the esophagogastric junction, the band of pressure usually is wider than normal, especially if hiatal hernia is associated. After deglutition the pressures in the upper part of the esophagus are normal However, in the lower half to two-thirds of the esophagus the peristaltic character of the response to swallowing is lost and replaced by a simultaneous rise of pressure which is often repetitive and of much greater amplitude than the peristaltic wave in health. Peristalsis is thus replaced by powerful simultaneous contractions low in the esophagus. The lower sphincter relaxes in response to the swallowing effort, just as in the healthy individual.

The treatment of diffuse spasm is most difficult Correction of an associated gastrointestinal disturbance is helpful in many cases. Some patients are improved by the passage of a 50-F. bougie Others may be helped by sedatives or by appropriate psychiatric therapy For a few individuals, a long myotomy extending well up the esophagus may be considered.

There are rare individuals who do not have clear-cut achalasia or diffuse spasm but have a motility pattern which contains some features of both conditions These patients with a "mixed" picture require a great deal of study.

SCLERODERMA OF THE ESOPHAGUS

Although scleroderma is not a common disease, it usually involves the esophagus, and dysphagia may be a prominent symptom. In some ways, the symptoms may be similar to those of achalasia. There is rarely much dilatation of the esophagus but in the advanced cases shortening of the esophagus takes place with regurgitation esophagitis, hiatal hernia and stricture.

Pressure studies have demonstrated that scleroderma of the esophagus is a disturbance of motility. In fact, there is frequently no evidence of peristaltic activity in the lower two-thirds of the esophagus. In advanced cases, there may be no zone of increased pressure between the stomach and esophagus. When this occurs, the sphincter does not function, and gastric contents may reflux. The treatment of scleroderma of the esophagus is principally the treatment of the primary condition. However, relief of dysphagia may be obtained by passing bougies over a previously swallowed thread This procedure may have to be repeated from time to time, especially in the patient who has a short esophagus and a stricture complicating the scleroderma.

COMPETENCE OF THE CARDIA AND ITS MAINTENANCE

Early in this chapter we devoted some attention to the anatomy and physiology of the lower sphincter of the esophagus. There is every reason to believe that a mechanism is present which prevents the regurgitation of gastric juices into the esophagus.[9] The competence of the cardia has been attributed to such factors as (1) a morphologic sphincter as described by Lerche, (2) an extrinsic sphincter, called "the diaphragmatic pinchcock," or a muscular sling formed by the right crus of the diaphragm and (3) a valvular mechanism related to the eccentric entry of the esophagus into the stomach As has been pointed out, the intrinsic pressure is higher in a zone at the esophagogastric junction than in either the stomach or the esophagus We believe that this physiologic sphincter is the most important factor in maintaining the competence of the cardia Any operative procedure which destroys this sphincter will cause incompetence of the sphincter. Even when esophagomyotomy for achalasia is carried out, it is important to



FIG 13—Diffuse spasm of esophagus (*A*) Diffuse irregular spasm (*B*) Diffuse constant narrowing (*C*) Pseudodiverticulosis (Reprinted through courtesy of publisher [12])

junction have been made before and after treatment by both dilatation and esophagomyotomy [13] The pressure at the sphincter which was elevated before treatment was markedly reduced after either endoscopic or surgical treatment However, while the increase in pressure was abolished in the suprahiatal portion of the sphincter, a definite elevation in the pressure persisted just below the diaphragm The preservation of this subhiatal portion of the sphincter is apparently important in the prevention of regurgitation esophagitis In particular, the surgeon must be careful to limit his incision to the distal part of the esophagus [3]

Diffuse Spasm of the Esophagus

The syndrome of diffuse spasm of the esophagus is less well known than achalasia or cardiospasm It has been called "nonsphincteric spasm," "segmental spasm," "pseudodiverticulosis," and sometimes "curling" or "corkscrew esophagus" Actually, the last two terms are most often used to designate the asymptomatic "tertiary" contractions seen by roentgenologists in older persons and after treatment of achalasia. Diffuse spasm is a spastic contraction of the distal half of the esophagus (FIG. 13) It was described by Moersch and Car in 1934,[10] and although the conditions a physiologically different, it has frequently be confused with achalasia (TABLE 1).

Pain is usually the most prominent featu in diffuse spasm The pain is substernal b may extend to the neck, jaws, ears, shoulde or arm It may closely resemble the pain coronary insufficiency Obstruction to swa lowing is a common feature, but these patien seldom regurgitate The condition occurs tense, nervous and emotionally unstable peo ple It often is associated with other disorder of the gastrointestinal tract, notably hiata

TABLE 1—*Differential Diagnosis of Achalasia and Diffuse Spasm*

Symptoms and Signs	Achalasia	Diffuse Spasm
Pain	Uncommonly	Almost always
Obstruction	Always	Sometimes
Regurgitation	Commonly	Rarely
Retention	Frequently	Never
Nervousness	Uncommonly	Almost always
Radiologic findings	Diffuse dilatation	Segmental spasm

Reprinted from Olsen and Creamer [11]

Hiatal Hernia and Its Complications

Although the physiologic mechanisms are not understood completely, it is well known that the cardia is incompetent in many cases of hiatal hernia of the sliding type. Most surgeons now recognize that the objective in repair of hiatal hernia is restoration of the competence of the cardia Esophagitis is a frequent complication of hiatal hernia The superficial, chemical and inflammatory reactions must be reversible. Ulcerative changes, however, may heal with cicatrization and result in both shortening of the esophagus and stenosis of the lumen above the gastroesophageal junction Such organic changes make conventional repair of hiatal hernia impossible.

Medical measures to prevent or control esophagitis include neutralization of gastric acids by antacid preparations. Reflux of secretions into the esophagus may be discouraged by elevation of the head of the patient's bed and by the avoidance of constricting garments about the abdomen. The obese patient must reduce his weight in order to reduce intra-abdominal pressure.

Treatment in cases of hiatal hernia with the complication of esophagitis is usually palliative. The endoscopist may keep the lumen open with dilatations carried out over a previously swallowed thread. Surgeons can resect esophageal strictures and at the same time attack the acidity problem by pyloroplasty, vagotomy or resection of the gastric antrum Currently, efforts are being made by surgeons to replace the shortened and strictured esophagus with some type of prosthesis. Portions of intestine may be brought up from the abdomen and used to replace or bypass the esophagus.

As yet no satisfactory substitute has been devised for the lower sphincter of the esophagus. Obviously, the best approach to these problems is prophylactic. The sphincter should be protected and preserved at all costs Operative procedures which destroy the sphincter must be avoided unless absolutely necessary Obviously, the sphincter must be sacrificed when operative procedures are performed for neoplasms in the junctional zone between the esophagus and stomach Benign strictures in the region, however, often can be treated successfully by dilatation.

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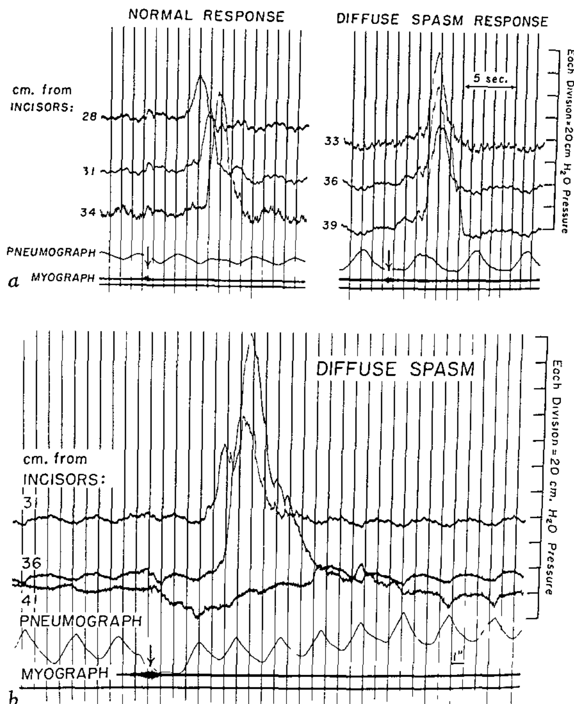


Fig 14—Deglutitory pressures should be at three sites in the esophagus (*A*) Normal response (*left*) and response in diffuse spasm (*right*) showing simultaneous waves which compared with the waves in the normal (*left*) (*B*) In lower part of esophagus and lower sphincter The wave of relaxation at the esophagogastric junction is similar to that in health (Reprinted through courtesy of the publisher [11])

leave a remnant of the sphincter in the subhiatal region.

Despite the major role of the physiologic sphincter in maintaining the competence of the cardia, anatomic factors also have considerable importance. Dislocations of the sphincter as with esophageal hiatal hernias may be responsible for reflux of gastric juice Intensive study of the lower sphincter, both in normal and abnormal locations, is needed

Intraluminal pressure studies in the lax esophagus,[5] and venous catheterization studies in mediastinal venous channels[7] are, however, providing excellent avenues for indirect investigation.

Mechanisms of Derangement of Normal Physiology

The pressure and volume relationships can be altered by a number of processes. Among these are expanding lesions within the space, which tend partially to obliterate it, tumors or chronic inflammation which may fix a portion of the expansile wall and convert the pulsatile movement into a torque, destruction of the normal intrapleural relationship, and exposure of the area to ambient pressure as in rupture of the esophagus, penetrating wounds of the neck or chest or spontaneous pneumothorax. It has long been noted that the speed with which these processes occur may be a more important factor than the degree to which they occur. The mediastinum can demonstrate a large degree of compensation to slowly progressing processes.

Interrelationship of the Mediastinum with Contained Structures

Effect of the Mediastinum on Great Vessels

Venous flow in the superior vena cava apparently is governed mainly by the existence of a favorable pressure gradient between the periphery and the right atrium. Normal respiratory activity cyclically alters the degree. This is true only when intraluminal resistance remains constant. Brecher, Mixer and Share[2] have demonstrated that this relation exists only during the beginning of inspiration. During the first part of inspiration the large part of the content of the jugulars is drawn into the intrathoracic segments and flow increases; however, when inspiration has reached a sufficient depth, further increase fails to occur. There is a depletion or segmental partial collapse of the extrathoracic segments, which increases resistance and prevents further increased flow. There remains the question whether increased inspiratory effort can partially overcome this tendency. Apparently, the amount of venous blood available to redistend these venous segments is the limiting factor in augmenting venous return. On the other hand, increased inspiratory effort may more completely deplete the extrathoracic veins with the net effect that the cardiac output is slightly increased, and more blood becomes available for venous replacement.

It has been demonstrated that intermittent positive pressure breathing without a negative phase may cause a decrease in venous return to the heart. This is of particular importance if hypovolemia exists, since a more marked decrease in venous return to the heart may occur. The negative phase of pressure breathing has been shown to implement venous return even in the face of hypovolemia.[7]

Venous return from the inferior vena cava is not only under the influence of the above-described mechanism, but also is dependent on variations in intra-abdominal pressure.[1]

Since pulmonary veins are entirely intrathoracic, respiratory variations in their flow probably reflect only the effect on the peripheral venous return to the heart.

Intra-arterial pressure is such that it is little affected by the relatively small variations in mediastinal pressure except indirectly when cardiac output is changed by variations in venous return.

Maximum expiratory efforts including cough, sneezing and the Valsalva maneuver cause considerable variations in mediastinal pressure,[5] and may also cause sharp decrease in cardiac output if prolonged or repetitive.

The thin walled veins are easily pulled, pushed, compressed or distorted by fibrosis, masses or unequally distributed pressure. These processes might well be expected to alter the venous return in the involved vessels.

The Effect of the Great Vessels on the Mediastinum

Disease of the great vessels, particularly disease of the aorta may disturb the pressure relations of the mediastinum. Aneurysmal dilatations or rupture of a vessel may produce expanding lesions which will act as any other expanding lesion depending on its location and rapidity of growth (see under Pressure Syndromes). A curious type of dysphagia occurs

Physiologic Disturbances in the Mediastinum

Some General Considerations of Normal and Deranged Physiology

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INTRODUCTION

THE mediastinum is a space containing many important structures in close relationship, and its physiology concerns the functions and interfunctions of the contained and surrounding structures It is an arbitrary space and not a definite anatomic structure. Nevertheless, the interrelationships of this space are of more than casual interest, and knowledge of it is not only important, but also frequently vital It is the purpose of this section to review the normal and abnormal interrelationships

BRIEF ANATOMIC CONSIDERATION

The mediastinum serves as a conduit for major vascular channels leaving and entering the thorax; also, it serves as a conduit for certain long nerve tracts including the vagus nerves, phrenic nerves and recurrent laryngeal nerves and for major structures as the heart, esophagus, trachea and main stem bronchi, and large aggregates of lymphoidal tissue The complex anatomic relationships of the space are beyond the scope of this discussion; however, certain considerations are of clinical import.

It is noted that the space has potential communication with the upper respiratory tract through the deep fascial planes of the neck, and a potential communication in its inferior aspect with the abdominal cavity and retroperitoneal space This relationship, of course, indicates pathways by which certain disease processes may reach the mediastinum from distant points. In addition, there is an inherent weakness in the lateral walls of the space in its anterior-superior and posterior-inferior aspects indicating directions into which herniations may occur and maximum shifts in position may result [5]

GENERAL PHYSIOLOGIC CONSIDERATIONS

The mediastinal space must allow for adequate and relatively frictionless function of its contained organs Many of these organs, including the heart, esophagus and root of the respiratory tree are dynamic structures and undergo variation in volume size and/or position during normal physiologic activity

The space itself is dynamic, changing its volume with phases of respiration Indeed, its maintenance as a space depends on the dynamic processes which maintain normal intrapleural pressure. It is relatively fixed in its superior aspect at the root of the neck and expands laterally with expiration and contracts with inspiration Elongation and increase in posterior-anterior diameter of the chest with inspiration more than compensate for the slight movement of the mediastinum toward the midline The variation in volume of the mediastinum is not without import Since the space is closed to ambient pressure, change in volume is accompanied by change in pressure within the space This periodic change in pressure exerts a massaging action on the venous return to the thorax, more specifically on the venous return from the head, neck and upper extremities [11]

The greatest handicap to knowledge of mediastinal physiology has been the lack of satisfactory methods for direct investigation As soon as the chest is opened or pressure devices introduced into the mediastinum, many of the normal relationships are destroyed

with pregnancy, abdominal masses or ascites, and depression of the diaphragms with emphysema partially interfere with this mechanism Unilateral splinting or paralysis of the diaphragm affects the mediastinum on the same side by interfering with the usual equal and synchronous changes in intrapleural pressure (see under Normal and Abnormal Movement of the Mediastinum).

Herniation of abdominal contents through the diaphragm, especially hiatal hernia, can act as filling defects in the mediastinum Disease of the retroperitoneal area may reach the mediastinum as previously mentioned. Pseudocysts of the pancreas and air from perirenal air studies have been reported as reaching the mediastinum

Diseases of the thoracic spine including cold abscesses, osteomyelitis, thoracic meningoceles and [illegible]

change the contour of the mediastinum

Funnel chest (pectus excavatum) may impinge on the anterior mediastinum and the anterior aspect of the heart, usually the right ventricle. If the defect is sufficient there may be mechanical interference with cardiac filling. The degree of impingement may be noted on the lateral chest film. Correction of more significant defects is best accomplished in the younger patient For objective comparisons one may measure the amount of water retained in the defect with the patient supine, allowing for slight increases as the patient grows. Pectus excavatum is discussed in detail in Chapter 43

Primary and secondary tumors, inflammation and infection of mediastinal lymph nodes frequently involve the space by continuity, and traumatic lesions of the chest may disrupt the thoracic duct permitting chylous outflow

Involvement of long nerve tracts will be dis- [illegible]

[illegible] in man. In cats there have been demonstrated branches of the vagi which end in a network throughout the middle mediastinum The fibers are difficult to differentiate from tracheobronchial fibers, but Widdicombe[14] has devised an arbitrary physiologic classification. Any receptor which is more sensitive to displacement of the mediastinum than to inflation or distention of airway passages by catheter is classified as a mediastinal receptor.

Normal and Abnormal Movement of the Mediastinum

The mediastinum is relatively fixed at the root of the neck. It has limitations of motion in the anterior-posterior direction due to the sternum and spine. Laterally it is bounded by more flexible structures and its greatest potential movement is in those directions, even though there is some restricting force. It has been noted already that the mediastinum moves toward the midline on inspiration and widens laterally on expiration. It also widens laterally in the prone position and moves to the dependent position in lateral recumbency [13]

Ordinarily, there is no significant shift of the mediastinum to either hemithorax during normal respiration. If there is disease in either hemithorax so that unequal presure develops, pendular motion may develop.

Samet and Anderson[15] describe five types of pendular motion of the mediastinum:

Type 1. On inspiration, the mediastinum is shifted toward the hemithorax which is the site of greater disease An expiration, this structure returns to the midline position The shift is evident by fluoroscopy but not by x-ray.

Type 2 This is identical with Type 1 except the shift is sufficient to be evident on x-ray.

Type 3. In this type there is shift of the mediastinum to the involved side on inspiration and to the opposite side on expiration

Type 4 Thi[illegible]

midline with inspiration and is moved to the opposite side on expiration.

Type 5 This type occurs with complete endobronchial stenosis The mediastinum is pulled to the diseased hemithorax on both inspiration and expiration.

If the mediastinum has been fixed or made

in vascular ring anomalies surrounding the upper esophagus[12] This syndrome is more likely to appear when the vessel is made rigid by arteriosclerosis.

The Effect of the Mediastinum on the Heart

The relation of the mediastinal pressure and venous return to the heart already has been emphasized Heart size and cardiac output are related to this directly. Reduction of heart size has been found in anesthetized and thoracotomized animals, and diastolic circumference of the heart has been found to be reduced by introduction of air into the pleural space

The Effect of the Heart on the Mediastinum

Patients with dyspnea associated with heart disease have been found to have altered elastic forces in the lung as reflected by the increase in pressure necessary to change the lung volume by a 100 cc increment[3] The maintenance of the mediastinum as a space depends on the *maintenance of normal intrapleural pressure* relations On certain occasions rapidly enlarging hearts or pericardial effusion may cause compression atelectasis in basilar segments of the lung The effect of atelectasis on movement and position of the mediastinum will be discussed in another subgroup An enlarged heart may also act as any mass and produce symptoms as described under pressure syndromes

The Effect of the Mediastinum on the Esophagus

The first wave of movement in the upper esophagus following the act of swallowing appears to be a negative wave of about 0 4 second duration Although it is not evident after each act of swallowing, it appears to be present with a fairly constant frequency There is a distinct possibility that this is related to a brief, reflexly induced inspiratory effort[4] The effects of respiration on emptying of the hiatal esophagus *have been a matter of controversy*, but it appears that reflux of gastric content occurs only during inspiration[6] The esophagus is readily compressible from without, and dysphagia is a frequent complaint with diseases of the mediastinum (see under Pressure Syndromes) Fibrosis near the esophagus from mediastinal disease may produce diverticuli of the traction type.

The Effect of the Esophagus on the Mediastinum

Dilatation of the esophagus is not an uncommon event in a wide variety of diseases of the esophagus including achalasia, strictures, carcinoma and scleroderma Dilatation of this organ acts as an expanding lesion within the mediastinal space Carcinoma of the esophagus frequently spreads locally to involve other mediastinal structures Rupture of the esophagus either spontaneous or induced is one of the commonest means by which the mediastinal space is exposed to ambient pressure.

The Effect of the Mediastinum on the Roots of the Bronchi

The roots of the bronchi can be pulled, pushed or fixed by disease of the mediastinum Tension on the external wall may produce cough and *abnormal respiratory sensations* Widdicombe[18] has demonstrated an elaborate set of vagal fibers in cats These fibers constitute a set of tracheobronchial receptors. A group of slowly adapting fibers is shown to initiate a cough reflex from distortion of the bronchial wall from without Partial obstruction from marked distortion is possible; this may also stimulate the set of fibers which are primarily stimulated from the luminal side

The Effect of the Roots of the Bronchi on the Mediastinum

If the mediastinum is free to move, it will move in the direction of greatest negative pressure Unilateral atelectasis secondary to bronchial obstruction will often create such a differential in pressure The effects of the bronchi and lungs on the mediastinum will be discussed in the section on normal and abnormal movements of the mediastinum

Other Relations

As the diaphragm descends with inspiration, the mediastinum is elongated, its volume is increased and its lateral wall moves toward the midline The opposite effects are noted with expiration Elevation of the diaphragm

with pregnancy, abdominal masses or ascites, and depression of the diaphragms with emphysema partially interfere with this mechanism. Unilateral splinting or paralysis of the diaphragm affects the mediastinum on the same side by interfering with the usual equal and synchronous changes in intrapleural pressure (see under Normal and Abnormal Movement of the Mediastinum).

Herniation of abdominal contents through the diaphragm, especially hiatal hernia, can act as filling defects in the mediastinum. Disease of the retroperitoneal area may reach the mediastinum as previously mentioned. Pseudocysts of the pancreas and air from perirenal air studies have been reported as reaching the mediastinum.

Diseases of the thoracic spine including cold abscesses, osteomyelitis, thoracic meningoceles, and neurofibromata frequently appear as masses in the posterior mediastinum. Kyphosis and kyphoscoliosis both directly and indirectly change the contour of the mediastinum.

Funnel chest (pectus excavatum) may impinge on the anterior mediastinum and the anterior aspect of the heart, usually the right ventricle. If the defect is sufficient there may be mechanical interference with cardiac filling. The degree of impingement may be noted on the lateral chest film. Correction of more significant defects is best accomplished in the younger patient. For objective comparisons one may measure the amount of water retained in the defect with the patient supine, allowing for slight increases as the patient grows. Pectus excavatum is discussed in detail in Chapter 43.

Primary and secondary tumors, inflammation and infection of mediastinal lymph nodes frequently involve the space by continuity, and traumatic lesions of the chest may disrupt the thoracic duct permitting chylous outflow.

Involvement of long nerve tracts will be discussed under pressure syndromes. The nerve endings in the mediastinum have not been well delineated in man. In cats there have been demonstrated branches of the vagi which end in a network throughout the middle mediastinum. The fibers are difficult to differentiate from tracheobronchial fibers, but Widdicombe[18] has devised an arbitrary physiologic classification. Any receptor which is more sensitive to displacement of the mediastinum than to inflation or distention of airway passages by catheter is classified as a mediastinal receptor.

Normal and Abnormal Movement of the Mediastinum

The mediastinum is relatively fixed at the root of the neck. It has limitations of motion in the anterior-posterior direction due to the sternum and spine. Laterally it is bounded by more flexible structures and its greatest potential movement is in those directions, even though there is some restricting force. It has been noted already that the mediastinum moves toward the midline on inspiration and widens laterally on expiration. It also widens laterally in the prone position and moves to the dependent position in lateral recumbency.[13]

Ordinarily, there is no significant shift of the mediastinum to either hemithorax during normal respiration. If there is disease in either hemithorax so that unequal presure develops, pendular motion may develop.

Samet and Anderson[15] describe five types of pendular motion of the mediastinum:

Type 1. On inspiration, the mediastinum is shifted toward the hemithorax which is the site of greater disease. An expiration, this structure returns to the midline position. The shift is evident by fluoroscopy but not by x-ray.

Type 2. This is identical with Type 1 except the shift is sufficient to be evident on x-ray.

Type 3. In this type there is shift of the mediastinum to the involved side on inspiration and to the opposite side on expiration.

Type 4. This type results from severe endobronchial stenosis with obstructive emphysema on the ipsilateral side. The mediastinum is midline with inspiration and is moved to the opposite side on expiration.

Type 5. This type occurs with complete endobronchial stenosis. The mediastinum is pulled to the diseased hemithorax on both inspiration and expiration.

If the mediastinum has been fixed or made

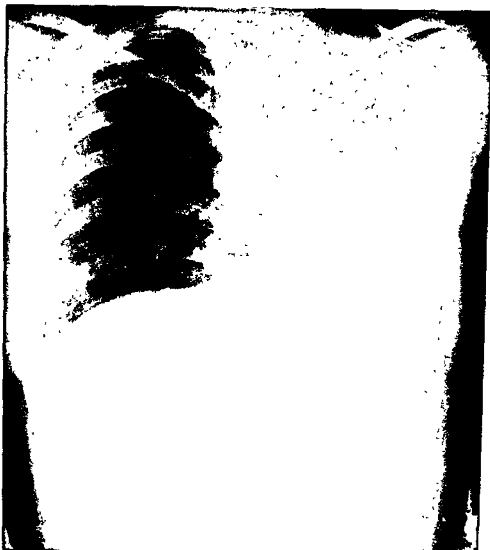


Fig 1—Mediastinal herniation simulating left lung

rigid by previous disease, the mediastinal shift may not occur.

If pressure changes are localized or the mediastinum is only partially fixed, herniation may occur in the regions of the anatomic weak spots previously described.

Figure 1 is a roentgenogram of the chest of a young housewife who had had a lower left lobectomy, and later an upper left lobectomy for severe bronchiectasis Later hemoptysis developed for which bronchoscopy and bronchography seemed to offer no explanation An anterior mediastinal herniation was demonstrated. It was so marked that the plain film suggested residual pulmonary tissue on the left side, but the bronchogram revealed that the right upper lobe extended well into the left hemithorax. Hemoptysis was thought to be related to congestion in the herniated segments

Fixation and Compression

The processes of fixation and compression are not identical They may occur concurrently or as separate processes In general, structures which are free to move and do so as part of their normal function are more susceptible to the physiologic effects of fixation. Structures which contain a lumen and have relatively flexible walls are more susceptible to the effects of compression.

Chronic infectious processes, such as tuberculosis, mycosis and occasional parasitic infestations, may exert their primary effects by fibrosis and fixation On the other hand, acute pyogenic processes may exert their influence

by rapid expansion and generalized toxic effects The fine areolar tissue of the mediastinum offers a poor barrier to the rapid spread of infection Although antibiotics are of prophylactic value and are an important adjunct in established disease, surgical intervention, prompt and adequate, is often necessary in the face of rapid, progressing infections of a pyogenic nature

A wide variety of *primary and secondary* tumors may be found in the mediastinum. It is noted that except for thyroid, parathyroid, rare intrathoracic pheochromocytoma and perhaps some thymic tumors, all of which are potentially active endocrinologically, the tumors of the mediastinum may be considered physiologically as a group. Their effects depend on their proximity to vital structures, degree of compression, invasion or fixation and above all on the rapidity of their growth.

Figure 2 is the chest film of a 68 year old veterinarian who was quite active, demonstrating the size to which these tumors may grow without crippling the patient, if they grow slowly. His only symptom was some nocturnal distress in the left lateral position

Emphysema

The pathologic physiology of free air in the mediastinum is a matter of some disagreement. Basically, the problem is difficult to approach without introduction of artificial



Fig 2—Mediastinal tumor with minimal symptoms appearing only very late in the course

mechanisms Karns[9] suggested that the air within the mediastinum may lead directly to circulatory embarrassment. Macklin[10] has suggested that in spontaneous pneumomediastinum air dissects along the perivascular sheaths of the pulmonic vessels from the alveoli to the mediastinum Pressure along the vascular sheaths, he believes, may be an important factor in circulatory embarrassment associated with pneumomediastinum Recently, Webb, Johnston and Geisler[17] have demonstrated, by injecting air into dogs and rabbits, that pneumomediastina in all are immediately decompressed by the air dissecting into the subcutaneous tissues or along fascial planes into the retroperitoneal space or rupturing into the pleural cavities Furthermore, they felt that the only significant circulatory and respiratory effects were due to secondary tension pneumothoraces

Pressure Syndromes[16]

Any mass arising in or near the mediastinum frequently exerts pressure on one or more of the contained structures Although the signs and symptoms usually occur in combination, we will discuss them under five main headings

Vascular compression is a frequent occurrence in mediastinal masses The superior vena cava is more susceptible due to its anatomic course, and compression results in cyanosis, edema and dilated veins of the face, neck, arms or thorax and dizziness, headache, tinnitus and even unconsciousness Thrombosis may ensue in the course of compression Minimal compression can be demonstrated by the appearance of the above signs and symptoms when the patient stoops over or raises his arms Rarely this may occur in a normal subject but will disappear almost immediately on resumption of the erect position Dyspnea and restricted motion of one side of the chest may result from hydrothorax or chylothorax resulting from compression of the pulmonary vein or azygos vein or thoracic duct

Compression on the root of the respiratory tree may result in tracheal deviation, coarse and medium rales either unilateral or bilateral Occasionally, unilateral expiratory wheeze is heard Dyspnea and orthopnea are not uncommon in compression of major bronchi but may also be on a circulatory or central nervous system basis Occasionally, dyspnea is present in only a lateral recumbent position A dry, persistent cough is quite frequent, and the cough may be "brassy" in major compression or involvement of the recurrent laryngeal nerves If erosion or invasion results, hemoptysis usually occurs.

Involvement of the long nerve tracts may occur singly or as mixed involvement Hoarseness or vocal cord paralysis may result from involvement of the recurrent laryngeal nerves. Horner's syndrome sometimes results from involvement of the sympathetic chain. Vagal pressure causes vomiting or reflex slowing of the pulse, and diaphragmatic paresis or hiccough may result from phrenic involvement

Gastrointestinal symptoms in addition to those listed above are primarily due to pressure on the esophagus Dysphagia and a sensation of strangling are frequent If severe compression results, overflow phenomenon occurs Reflux esophagitis occurs if the lower end of the esophagus becomes distorted so as to make the cardia incompetent

Pain is a prominent symptom in mediastinal compression It is not the purpose of this section to go into the details of mechanisms of mediastinal pain Pain may result from pressure or traction on long nerve tracts or on pain-sensitive endings in certain other structures under tension The pain may be fairly well localized or referred Erosion of bony structures tends to produce a rather localized type of pain Referred pain is somewhat difficult to differentiate, since pain for tumor growths may simulate angina of coronary origin

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Section XII

THE RELATION OF SPECIAL ENVIRONMENTAL INFLUENCES TO CARDIOPULMONARY PHYSIOLOGY

COMMUNITY DISASTERS

Several disasters resulting from the combustion of community air pollution and extremely adverse climatic conditions have already occurred.

During the first week of December 1930, dense fog coupled with a temperature inversion covered the Meuse Valley in Belgium, holding down the air pollutants from local heavy industry. Beginning on the third day, thousands of persons became ill with respiratory complaints Sixty died—ten times the number expected under ordinary circumstances Symptoms included throat irritation, cough and shortness of breath Most of those who died were elderly persons with chronic cardiac or pulmonary disease The causative agent was never finally determined although sulfur dioxide and sulfuric acid were suspected, along with particulate metal oxides

London experienced heavy fog associated with air pollution, December 5–9, 1952 An unusually high frequency of illness and mortality beginning within a day after the onset of the adverse atmospheric conditions was not fully recognized until a survey was carried out later Then it was found that hospital admissions for respiratory and cardiac disease had risen sharply and that about 4,000 deaths in excess of the number expected had occurred in London during the fog and the week following Infants as well as older persons were particularly affected Those living in central London suffered to a greater extent than those in the outlying regions In addition to the unfavorable climatic conditions of fog and low temperature, pollution with sulfur oxides and solid matter in coal smoke and possibly other substances were considered contributory. A subsequent episode, in 1956, claimed about 1,000 lives; studies have revealed what were probably comparable episodes as far back as 1873

Community outbreaks of asthma have also been attributed in some instances to air pollution. "Yokohama asthma" was the name given to a disorder recognized early in the winter of 1946 among American servicemen and their dependents in Yokohama During the preceding year, many of the personnel had experienced a mild bronchitis; in 1946, they had attacks of wheezing and shortness of breath typical of asthma. Most of those afflicted had no history of allergy. The attacks occurred during a period of low winds and much air pollution.

American newspapers carried during 1958 the story of another in the series of outbreaks of asthma in New Orleans. The epidemiologic picture is a sudden large increase in the number of persons seeking hospital attention for asthma attacks, starting late in the evening and continuing for several hours thereafter. It is difficult to conceive of any factor that would have had such an effect other than a sudden change in the environment, probably of the atmosphere.

The last week of October 1954, with a temperature inversion and low wind, contributed to the accumulation of industrial pollutants in Donora, Pennsylvania, a town located in a steep valley along a bend of the Monongahela River. More than two-fifths of the population suffered symptoms, beginning on the second day and including sore-throat, cough, tightness of the chest, headache and dyspnea. Fifteen deaths occurred, mostly among older persons with cardiopulmonary disease. Again, sulfur oxides and particulate matter were blamed for the ill effects, although the evidence was not clear.

In addition to the problem of atmospheric contamination affecting a whole community, chemical substances which are accidentally released by industrial process may injure persons located close to the plants As technology advances, the amount and types of such substances will increase so that protection for the community against health hazards of this sort will become an increasingly difficult engineering and public health problem. Two accidental episodes have been carefully investigated, and they provide evidence of the potential problems to be anticipated.

In Poza Rica, Mexico, a city of 22,000 persons in the heart of Mexico's oil and natural gas-producing area, a portion of a new plant for the removal of hydrogen sulfide from natural gas went into operation, Novem-

Atmospheric Conditions of Cities

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THIS chapter on atmospheric conditions has been written for *Clinical Cardiopulmonary Physiology* to emphasize that the passage of foreign constituents into the respiratory system may play an extremely detrimental role in the development and progression of chronic pulmonary disease It is realized, naturally, that physiologic testing in itself may not reflect the specific influences of atmospheric conditions However, knowledge of the atmosphere often will prove invaluable for determining the exact status of disability and the most effective type of treatment

Introduction

For centuries people and their physicians have noted the health effects of various climates The influence of both natural and man made climate has been considered especially great on pulmonary symptoms and disease

Eruption of volcanoes has caused deaths, among other ways, by atmospheric pollution arising from these catastrophes In recognition of a more common effect of natural climate, physicians often advise patients with severe respiratory disease to avoid cold, moist climates and to seek residence in warm, dry areas

Pollution of the atmosphere arising from man's own activities, especially since the industrial revolution, has had a deleterious effect on life in cities Burning of fuel has been a major source of such pollution coal at first, and still today; then petroleum, and now the hazards of nuclear reactors are beginning to appear

England has endured the pall of coal smoke over her cities since the thirteenth century when the first complaints in London were recorded. Only with control of the epidemic communicable diseases has the full impact of air pollution on residents of London and other cities of England become apparent This has taken the form of extremely high rates for chronic bronchitis and other chronic pulmonary diseases Until recent clean-up campaigns, American cities, too, e g, St Louis and Pittsburgh, have experienced heavy pollution from coal smoke

Thus, coal burning and other side-effects of industrialization have exacted not only a substantial toll of discomfort for living in heavily polluted sections of cities, but more importantly higher rates of disease, and even death With aging of the population and consequent longer exposure of masses of people to these damaging influences, the effect has lately become more obvious The current acceleration of technologic change complicates the situation and adds to the hazard

Extensive use of petroleum as a fuel in industry and particularly in motor vehicles has produced an extremely bothersome type of air pollution in Los Angeles and other cities of western United States This variety of air pollution is only now being assessed for its possible relationship to cardiopulmonary function

Rising levels of radioactivity in the ambient air due to man's increasing use of nuclear energy, demand that attention also be given to this type of pollution as a hazard to pulmonary tissue, as well as to blood cells and other tissues

During each day, the average person inhales about 30 pounds of air, compared with the ingestion of less than 4 pounds of food and 5 pounds of water The pulmonary route is a common one for the ingestion of toxic substances affecting several organs Familiarity with substances in the air and their physiologic fate is therefore of considerable importance to medicine

spiratory tract. Efforts to assess possible adverse effect have been accelerated in recent years through increasing interest on the part of many investigators, the establishment of a program of study by the California State Department of Public Health and the initiation of a research program by the U.S. Public Health Service.

First attention was given to the question of whether air pollution episodes of the type and degree experienced in Los Angeles caused an immediate increase of mortality. Examination of mortality data up to the present time has provided no clear evidence that the number of deaths increases during periods of air pollution Since it appears from investigations of community disasters elsewhere that elderly persons with diminished cardiopulmonary reserve are most susceptible to air pollution, special analyses of the experience of such populations in Los Angeles have been undertaken For example, during the summer and fall of 1954 three distinct "smog" episodes each lasting several days, affected Los Angeles. The daily number of deaths among persons 65 years of age or older in the community did not appear to fluctuate in response to these episodes However, the number of deaths in this population did appear to increase when the temperature rose above 100 F for several days in 1955 In a further attempt to assess the immediate mortality effect of air pollution, the deaths among approximately 4,000 residents of Los Angeles nursing homes have been studied continuously since 1954. The persons under observation for the most part are past 70 years of age and enfeebled by cardiopulmonary as well as other types of disease. As yet no increase of mortality in this population has occurred in relation to episodes of air pollution. The susceptibility of this population to atmospheric conditions, however, is demonstrated by the ninefold rise in mortality associated with the September 1955 "heatwave" in Los Angeles when the temperature exceeded 100 F. for several days (FIG 1)

Another effort to ascertain whether there is an acute effect from Los Angeles type air pollution on human health consisted of a study of the frequency of asthma attacks in relation to the intensity of air pollution During the fall of 1956, for 15 weeks, 137 asthma patients under the care of five physicians and living in a section of Los Angeles with heavy air pollution kept a record of the hour and day of each episode of asthma. Analysis of the data revealed the peak hours for asthmatic attacks to be midnight to 6.00 a.m. The lowest frequency occurred at noon to 6:00 p m. when "smog" is usually more severe. No definite increase in the number or severity of asthma was associated with the degree of air pollution on the same or preceding day.

Additional data bearing on the possible effect of Los Angeles air pollution on pulmonary manifestations are noted in the California Health Survey.[3] This is a household survey in which census-type interviewing of a representative sample of the population provides data on the occurrence of illness and related matters During the relatively severe air pollution episodes in 1954, the frequency of such illnesses as colds, asthma, hay fever and other respiratory conditions did not increase. Likewise, there appeared to be no rise in the rate of hospital admissions for cardiac or pulmonary disease.

Although analysis of data available up to the present time does not indicate a gross, immediate effect on mortality or cardiopulmonary disease resulting from Los Angeles air pollution, certain limitations of the investigations should be emphasized The statistical methods of analysis may fail to disclose subtle mortality effects Also the observations reported have been limited largely to mortality and morbidity. Still to be reported are several studies of pulmonary function itself and its relationship to air pollution. Finally, the indices of air pollution are still quite crude and may not be sensitive to the particular agents causing an effect on cardiopulmonary function. Efforts to remedy the possible defect in the studies, by improving the statistical design of the studies are under way.

The possibility still exists of a community disaster from severe air pollution of the Los Angeles type occurring at the time of extremely adverse atmospheric conditions For

ber 21, 1950 During the nights of November 23–24, the flow of gas through the plant was increased at a time when the weather was foggy with a low inversion layer of low winds Between 4·45 a m and 5:10 a m., nearby residents were afflicted with respiratory and central nervous system symptoms. Three hundred and twenty were hospitalized and 22 died. Among 47 of the hospitalized persons who received close study, all lost the sense of smell, two-thirds had severe headache, one-half became unconscious and about one-third were affected by dyspnea, cough and nausea. Necropsy showed pulmonary edema and congestion, cerebral congestion and punctuate hemorrhages

On October 10 and 11, 1957, at the nuclear reactor station in Winscale, England, the graphite pile overheated and fission products passed into the atmosphere through the air cooling system According to a British White Paper there was no harm to personnel or surrounding population Radioiodine (I^{131}) was emitted, along with lesser amounts of radiostrontium and radiocesium Since radioactivity in the milk of the area rose to 0 8 microcuries per liter, distribution of milk from this area was suspended until such time as the level decreased to less than 0 1 microcuries per liter Examination of water, meat, eggs and vegetables revealed no apparent hazard due to the ingestion of these substances It was considered necessary to check periodically the strontium-90 content of milk from cattle grazed in the areas affected

THE LOS ANGELES PROBLEM

Since the 1940s, Los Angeles has suffered a type of air pollution characterized by reduced visibility, eye irritation and damage to vegetation Although the term "smog" has been applied to this condition, neither smoke nor fog is essential to it. As a matter of fact, Los Angeles air contains less smoke than that of many other large cities in the United States

The pollution consists of a complex mixture of gases, solid particles and liquid droplets An important feature is the oxidation of hydrocarbons in the presence of sunlight and oxides of nitrogen. This chemical reaction in the air produces many substances, some of which are irritating to the eyes and produce plant damage. Hydrocarbons for the reaction come from unburned or partially burned petroleum released to the atmosphere to a large extent from automobile exhaust. About 7 per cent of the gasoline escapes from automobiles in this form, resulting in the discharge into the atmosphere of more than 1,000 tons of hydrocarbons on an average day Generally, the most irritating effect occurs when sunlight is greatest, e g, during the summer and early fall and during the middle of each day. However, eye irritation can be considerable when the sunlight is largely obscured by haze or clouds The problem is emphasized by the number of motor vehicles licensed in Los Angeles County. in 1930 there were 871,773; in 1940, the number was 1,229,194, and by 1956 the number had increased to 2,728,439.

In addition to the type of atmospheric pollution encountered in Los Angeles the air may also contain certain metallic and other foreign substances in the form of hundreds of compounds whose nature and effect are as yet little understood

The accumulation of these pollutants is favored by low winds, sunlight and an inversion of the normal temperature gradient in the atmosphere which impedes the upward flow of contaminants—in effect putting a gigantic lid over the basin in which lies Los Angeles with its five million persons, its teeming industry and the profusion of automobiles

Although Los Angeles has attracted most attention for this type of air pollution, the condition is by no means limited to that community It has been occurring with increasing intensity elsewhere in California and other parts of the United States Los Angeles air pollution may be merely a prototype for what will affect other metropolitan communities with the growth of automobile traffic and other factors, unless control measures are established

Besides immediate interference with well-being, i e, eye irritation, nose and throat irritation and other disagreeable symptoms, air pollution may also cause more profound damage to health. Of particular concern is the re-

spiratory tract. Efforts to assess possible adverse effect have been accelerated in recent years through increasing interest on the part of many investigators, the establishment of a program of study by the California State Department of Public Health and the initiation of a research program by the U S. Public Health Service.

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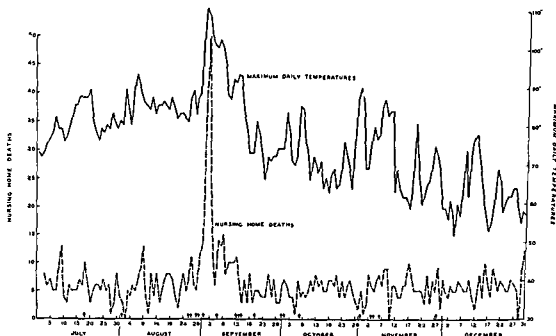


Fig 1 —Nursing home deaths, maximum daily temperatures and smog alert days (Los Angeles County, California, July, 1955 through December, 1955) Arrows indicate days of official alerts (ozone PPM or higher)

this reason as well as others, continuing surveillance of the problem is essential

Prevention and Treatment of Acute Effects of Air Pollution

The one completely satisfactory way to avoid the effects of air pollution on health is to prevent the emission of man made pollutants. Application of this principle is limited by present knowledge about how to conduct industrial processes and burn fuels without adding harmful substances to the air The development of the engineering skills for preventing pollution in such organizations as the Los Angeles Air Pollution Control District and the industries with which it has consulted is a very impressive achievement Apparently, the only major uncontrolled source in that community in 1959 was exhaust from automobiles. Control at the source presents some unique problems and is almost certain to be costly.

In varying degrees the air of an enclosed room or building can be purified with various types of equipment Standard air conditioners usually contain a fiberglas filter which is capable of removing the larger dust and pollen particles as well as a portion of the smaller aerosols of the size found in tobacco smoke (about 0 7 microns) However, these standard air conditioners are not effective in removing the eye-irritating or plant-damaging substances characteristic of Los Angeles smog Activated charcoal filters are effective for this purpose and may be used with standard air conditioners In addition to aerosols, they also absorb gases and vapors

At the time of the London disaster in 1952, prize cattle at a livestock show whose stalls were kept spotless had greater fatalities than stock whose stalls were not so clean The latter may have been protected by ammonia released from their excreta, since ammonia will neutralize acid gases and vapors such as sulfur dioxide A suitable wick dispensing dilute ammonia gas can in fact counteract the irritating and bronchoconstructive effects of sulfur dioxide and sulfuric acid mists It is said that a baby with wet diapers will substitute nicely for the wick.

Though gas masks of various types can remove most foreign substances from the air to be breathed, they have not proved a suitable method for protecting susceptible persons from air pollution The reason is that susceptible persons usually have impaired respiratory mechanics and the added work of breathing through a mask is not well tolerated

Bronchodilator drugs of various types have been tried for prevention and treatment of air pollution effects. Conclusive results are not yet available.

Chronic Disease Effects

Besides the immediate adverse effects of air pollution, there may be long-term influences of even greater consequence. In particular, chronic irritation of the respiratory tract by pollutants must be considered a possible cause of pathology and disturbed pulmonary function

Investigation of such effects has followed several paths One has been chemical analysis of substances found in the air Studies of air chemistry in various cities of the world have revealed the presence of heavy metals including lead, arsenic, iron and magnesium, hydrocarbons such as 3,4-benzpyrene and others known to be carcinogenic; oxides of sulfur and nitrogen can be highly injurious to the respiratory tract if present in sufficient quantities, also, aldehydes such as acrolein, used as a tear gas in World War I, carbon monoxide, the well known asphyxiant, particulate matter and other pollutants The physical characteristics of the substances present, as well as their chemical nature may play an extremely important role in determining whether adverse effects occur. For example, certain gaseous substances, harbored in the nose or upper respiratory passages may combine with minute particles of solid matter or liquid droplets (aerosols) from the air. In this form they may penetrate deeply into the respiratory tract and thus cause greater damage than would be expected in their gaseous state. Although progress is being made at the present time toward a better understanding of the physical-chemistry of the air, and the possible relationship to health of various substances identified in the ambient air, this field is still in its infancy One difficulty in the investigation is the extremely dynamic character of the reactions in the air By the time a sample of air has been collected and transported to a laboratory for study, extensive changes in some constituents have already occurred

In addition to this chemical approach to the problem, another line of investigation has been to expose animals under experimental conditions to substances found in the air Certain hydrocarbons isolated from the air of Los Angeles and other metropolitan communities when applied in concentrated form to the skin of animals will cause malignant growths Exposure of guinea pigs to ozone in concentrations of one part per million six hours per day for about a year produces pulmonary fibrosis, and exposure to higher levels of ozone results in fatal pulmonary edema

Lung Cancer

Although cigarette smoking is now generally considered as the major factor in the sharp increase of lung cancer during recent decades especially among males of many countries, cigarette smoking does not account for all cases of this disease. Indeed, some cases of the disease have been clearly associated with occupational exposures, *e g*, in certain chromate ore operations and in the Schneeburg mines

The possible role of community air pollution in causation of lung cancer has likewise been receiving considerable attention Several lines of evidence support the view that it may be a factor

Chemical studies of the air in cities of many countries (England, U S A , U.S.S R ,[11] and others) have revealed the presence of known carcinogenic substances These include hydrocarbons such as 3,4-benzpyrene and certain heavy metals including arsenic Although some measurements have been made, it is not clear that the amounts present are sufficient to induce human lung cancer However, experimental animal work has demonstrated that concentrates of substrates taken from the atmosphere will produce tumors in animals Again, the question of dosage as well as the problem of interpreting animal studies in the light of human experience makes this type of evidence by itself, though strongly suggestive, inconclusive

Epidemiologic observations also add to the picture Numerous studies in several countries have made it clear that lung cancer mortality occurs much more frequently in cities than in rural areas Furthermore, mortality from the disease is higher in sections of cities in

which air pollution is greater than in sections where it is not so severe. Although cigarette smoking is more common among city dwellers than among rural people, studies both in the U S and England indicate that the difference in cigarette smoking will not account for the entire excess of lung cancer in cities The role of specific occupations has not been fully determined One investigation in New Zealand showed an excessive mortality from lung cancer among immigrants from Great Britain, especially among persons who had migrated after reaching the age of 30 years This excess, which did not occur in the case of other sites of cancer, could not be attributed to differences in cigarette smoking It was, therefore, suggested that air pollution in cities of Great Britain may have played some role prior to migration to New Zealand

Thus, data from chemical, experimental and epidemiologic investigations are all consistent with the view that the air pollution of cities may be one factor in lung cancer

Chronic Bronchitis and Pulmonary Emphysema

In Great Britain a disease called chronic bronchitis is among the most common causes of morbidity, especially in males 40 to 65, and in this group it is second only to arteriosclerotic heart disease as a cause of death

Since mortality from chronic bronchitis is much lower in the United States, and also substantially lower in countries of Western Europe than in Great Britain, it is useful to examine the criteria on which the diagnosis is made

The disease ordinarily starts with a cold in the chest, after which cough and sputum continue. With repeated episodes, coughing becomes accentuated and persists It is then usually characterized as worse in the morning followed by one or two severe bouts daily with increased purulent sputum, susceptibility to intercurrent respiratory infection is marked In time, bronchospasm and shortness of breath develop In the later stages of chronic bronchitis, there may develop emphysema and cor pulmonale.

Since, in the United States, pulmonary emphysema is frequently mentioned as the cause in deaths, most closely corresponding to deaths ascribed to chronic bronchitis in Great Britain, it is of interest to study the incidence of pulmonary emphysema in the United States In California during the period of 1950 to 1957, this cause of death has increased about fourfold in each of three age groups A number of possible explanations for this apparent epidemic of a chronic disease should be considered:

1 Deaths which in 1950 would have been certified as due to asthma, bronchitis, bronchiectasis or chronic pneumonia are now being ascribed to emphysema as the cause of death
2 The increase reflects the migration of persons with this disorder to California where they die
3 Persons who formerly died of pneumonia, influenza or tuberculosis now survive these diseases to die of pulmonary emphysema
4 There is a true increase in the condition

The first explanation is unlikely because there has been no decrease in the other diagnoses as causes of death during the period The second explanation also is unlikely since a similar process has occurred in New York State

While in California there is no important difference in emphysema death rates between metropolitan and nonmetropolitan parts of the state, this is not true in other parts of the country In fact, pulmonary emphysema was about twice as prevalent in 1950 as a cause of death in metropolitan areas as in nonmetropolitan areas

Most of the epidemiologic studies of chronic bronchitis and emphysema have been carried out in Great Britain Fairbairn and Reid,[4] for example, have studied the association in Great Britain of mortality from certain respiratory diseases with indices of environmental conditions The mortality has been significantly associated with the fog index Reid has also shown that the frequency of lost time and premature retirement among postal workers due to chronic bronchitis is significantly associated with air pollution. Furthermore, the workers who carry mail in heavily polluted areas are more severely affected than those who work in less polluted areas, and indoor workers in

polluted areas are less affected than outdoor workers.

A simple but effective method for studying the aggravation of chronic bronchitis by air pollution was developed by Lawther in England[6] He asked patients with this disease to mark in a diary each day whether they were better, about the same, worse or much worse than usual He then averaged these values and was able to show, e.g, that in January 1956 when sulfur dioxide and smoke increased a great deal, the "degree of illness" also increased This method is now being further tested, both in California and in Great Britain

These findings indicate that the chronic bronchitis syndrome may be caused and aggravated by the unhygienic conditions of the air in British cities So far there is not sufficient data to draw such a conclusion about the chronic obstructive pulmonary disease syndrome in the United States. Pemberton[8] has shown that elements of the syndrome are more common in coal workers in the U S than in industrial workmen in either of two New England towns. It is widely believed that cigarette smoking also plays a part in chronic obstructive pulmonary disease but critical data are scanty.

The clinical and physiologic features of chronic bronchitis are discussed in Chapter 46

Berylliosis

The history of berylliosis illustrates only too well the danger of chronic pulmonary disease arising from new substances released into the air, both inside and outside industrial plants, as a consequence of technological advances

During the development of the fluorescent lamp industry, beryllium came into use as a key material in their manufacture In 1943 a monograph on the toxicology of beryllium gave it a "clean bill of health," based on certain experimental animal studies Only the acid compounds of beryllium, particularly the fluorides, were suspected of being injurious When the first cases of chronic pulmonary fibrosis appeared among the workers in the fluorescent lamp industry, beryllium was not immediately considered as the offending agent. However, when similar lung changes were discovered among persons exposed to beryllium-copper alloy fumes, investigators recognized beryllium oxide as the toxic material in both situations Meanwhile, persons merely living in the neighborhood of the plants in which beryllium was used in manufacture became chronically ill with berylliosis

Thus, it is necesary to maintain constant vigilance concerning potential damage to pulmonary as well as other tissues resulting from new chemicals released to the air, both inside and outside modern industrial establishments

The clinical and physiologic features of berylliosis are described in Chapter 51

The Significance of Aerosols and Particle Size

Research is continually adding to our knowledge about the effects of air pollution on health and the mechanisms which underline these effects The capacity of aerosols to enhance the physiologic effects of gases in guinea pigs is of special importance Amdur[1] at the Harvard School of Public Health has developed a standardized method for measuring the change in flow resistance in the lungs of guinea pigs in response to various inhaled substances Her studies indicate that the presence of an aerosol composed of droplets of sodium chloride solution 0 2 microns in diameter increases the response to sulfur dioxide, and also to formaldehyde The increase is proportionately greater at low concentrations, e g , 2 parts per million of gas plus aerosol gives a response equal to 60 to 70 parts per million of gas alone

Since most air pollution disasters have been associated with foggy weather, it seems possible that the aerosol in fog is an important feature in the effect produced

It has been noted in the study of aerosols containing particles of various sizes that particles 4 or 5 microns in diameter are removed completely or deposited temporarily in the mucosa of the nose, throat or upper airway before the incoming air reaches the alveoli of the lungs The aspects are presented visu-

ally in FIGURE 2 Those of intermediate size, about 2 microns in diameter, are removed for the most part in the bronchi by impaction into the mucus blanket which is constantly being displaced proximally by ciliary activity. The particles most likely to be retained in the alveoli or terminal bronchioles through impaction on their walls are about 0 2 microns in size, but such particles, even the smaller size, usually remain suspended in the air and eventually will be exhaled without even touching the tissues of the lung into whose labyrinth they were aspired However, of those retained many will reach the alveoli and alveolar ducts; and thus the size of an aerosol may be of great importance in respect to the type and dose of polluting material actually breathed In addition, since the air becomes uniformly saturated

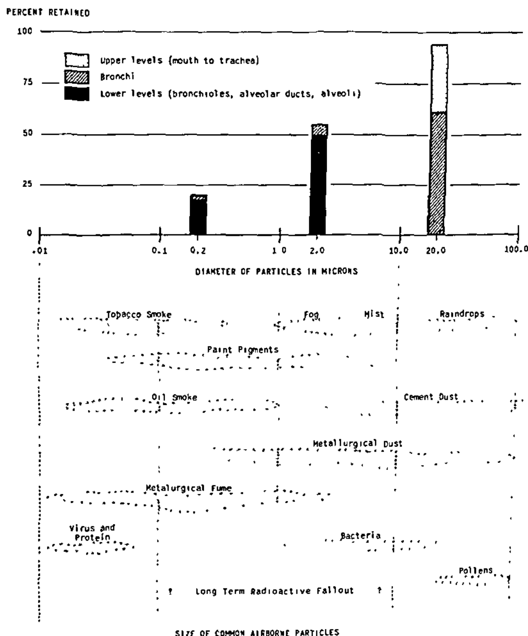


FIG 2—Relationship between particle size, origin and pulmonary retention Theoretical percent retention of particles at several anatomic levels of the lung and airway (From LANDAHL, H D, AND HERMAN, R G On the retention of air borne particulates in the human lung J Indust Hyg & Toxicol. 30 181, 1948)

with water vapor as it travels distally in the lung, a particle may increase in size by absorbing water as it passes further down into the airway.

Atmospheric Conditions of Cities—A New Challenge to Medicine

When the industrial revolution brought masses of people together in cities, the first major health problem was contamination of water supplies which resulted in cholera, typhoid and other intestinal diseases These continued to strike metropolitan communities in epidemic form until the current century In the case of pulmonary disease, tuberculosis has been the leading problem, until more recent years it was aggravated by industrial living conditions. A profound change has occurred in the health picture and medical practice of the United States and other industrially advanced nations No longer do communicable diseases plague the family and the community However, unsavory factors have entered the atmosphere, posing countless problems that call for prompt and careful investigation The medical profession rightfully should look to the engineering sciences for the earliest possible control or eradication of atmospheric contaminants

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Altitude Physiology: Air Travel in the Jet Age

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THE earliest manlike creatures doubtless looked with wonder at the beauty of the sky and perhaps, even as the child of today, dreamed of emulating the birds in their flight. As he grew in intellectual capacity, man ascribed to the Gods in the heavens the seasons of the year, the success or failure of his ventures and guidance over his everyday life. It is possible that man's urge to reach ever higher into the sky may indeed have very deep roots in his dreams, aspirations and even perhaps in his religions for ages past. However, from the earliest man who dreamed of soaring aloft, to the aeronautic and astronautic engineer or aviation medical specialist of today, the most disenchanting reality is the rapidly increasing hostility of the environment as man proceeds higher from the earth's surface where he evolved. Indeed, this has only been made possible by devising many complex supporting pieces of equipment to enable him to survive at ever increasing heights.

The first successful flight by the Wright Brothers at Kitty Hawk occurred in 1903, less than 60 years ago. Since that time, there has been enormous progress in aviation, particularly during the past 25 years.

Man's efforts to rise into the sky first attained a measure of success using large balloons filled with warm air. Later, hydrogen-filled balloons were used, and by means of these, man was able to reach altitudes which disclosed the problems due to diminished air density, pressure and temperature.[1] For some years past, balloons and later dirigibles appeared obsolete in the face of the rapid developments in powered flight. Recently, however, balloons filled with helium have again become of upmost importance in high-altitude research, in the vicinity of 100,000 feet or more.[22, 24, 27]

FIGURE 1 indicates the developments in aviation,[17] as reflected by the speeds attained chronologically since the Wright Brothers' exploits at Kitty Hawk. The record of 2,148 miles per hour was attained by Captain Apt of the United States Air Force in his ill fated flight in September, 1956. Captain Apt's record speed should be compared with the two critical speeds of importance in the conquest of space. Speed for orbital vehicles is 18,000 miles per hour, and for escape into space, speeds of 25,000 miles per hour are necessary (FIG. 2). It may be anticipated that man will probably attain approximately orbital flight speeds by 1960 or 1961 if present efforts continue.

In terms of altitude, the flight of the late Captain Iven Kincheloe, United States Air Force, also in September, 1956, reached the record altitude of 126,000 feet (FIG. 3). At this altitude, over 99 per cent of the mass of the atmosphere had been penetrated. For many practical purposes, Captain Kincheloe may be said to have been the first man to reach space equivalent conditions.[7, 30]

These notable military achievements came from the combined efforts of many scientific disciplines teamed with engineering, medical, technical and manufacturing skills. The applications of this costly research also led to corresponding improvements in civilian com-

mercial aviation, the latest development being the turbo-jet powered airliner This brings within reach of travelers speeds at altitudes undreamed of only a few years ago, together with far reaching effects on our concepts of time and distance. These speeds can only be obtained economically at considerable altitudes because of diminished air friction and the fact that turbo-jet engines achieve their best economy of operation between 30,000 and 40 000 feet. Thus, in considering the new hazards associated with high-speed, high-altitude flight by commercial airliners, we will draw heavily on military experience and research, since these problems have been known in military aviation for some years The purpose of this chapter is to provide some general understanding of physiologic and other stresses which can occur as a direct result of flying at high altitudes, and something of the measures taken to safeguard both passengers and crews against these stresses

The extraordinarily rapid increase of acceptance of air travel during recent years is shown in FIGURE 4 For comparison, this is shown in relationship to the population of the United States This conveys some idea of the numbers of individuals who can be exposed to hazards implicit in flying at jet airliner altitudes in the future, as well as enjoying the many advantages of very high-speed, high-altitude flight Allowance must be made, of course, for those who will make several flights each year.

The atmospheric envelope surrounding the earth is said to weigh about one-millionth the weight of the earth Minute traces of atmosphere are found at altitudes of well over a hundred miles For purposes of convenience, it has been divided by physicists into layers.

Troposphere This is the layer next to the earth in which there is seasonal influence and geographic variation

Tropopause This is a transition zone averaging about 35,000 feet in the temperate zone

Stratosphere Above 35,000 feet the temperature is around minus 65 to 75 F, winter and summer—somewhat colder over the equator than over polar areas Here, there is little turbulence as a rule and the humidity is quite low Modern turbo-jet airliners will fly in the tropopause and stratospheric regions

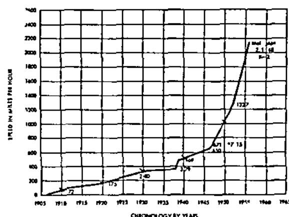


FIG 1—Speed achievements plotted chronologically (Reprinted through courtesy of the publisher[7])

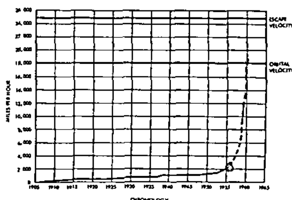


FIG 2—Speed achievements plotted in relation to orbital and escape velocity (Reprinted through courtesy of the publisher[7])

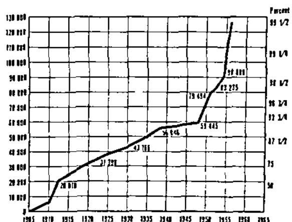


FIG 3—Altitude achievements plotted chronologically Highest is Captain Iven Kincheloe's flight to 126,000 ft (Reprinted through courtesy of the publisher[7])

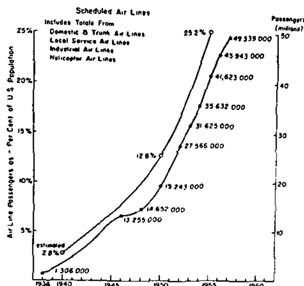


FIG 4—Scheduled Airlines Includes totals from Domestic and Trunk Airlines, Local Service Airlines, Industrial Airlines and Helicopter Airlines (1938–1957 data from 19th Edition, "Air Transport Facts and Figures" from "American Aviation," 21 April 1958 Published for Air Transport Association of America)

Above this is the *chemosphere*,[9] *ionosphere*,[15] and *exosphere*,[15] which are at extreme altitudes and at the edge of space.

The density of the air diminishes with altitude as a result of decreasing pressure This, in turn, follows from the lesser weight of the diminishing column of air above There is poor acoustic conductivity, as a result of which the quality of the voice changes and hearing is diminished Coughing is also less effective

The pressure of the air likewise diminishes with altitude. This is the primary cause of hypoxia and decompression sickness It was the cause of the difficulties and tragedies experienced by the early balloonists,[1] some of whom reached altitudes of 28,000 and 29,000 feet.

At sea level	One atmosphere 14 7 lb per sq inch or 760 mm Hg
18,000 feet	One-half atmosphere or 380 mm Hg
34,000 feet	One-fourth atmosphere or 190 mm Hg
48,000 feet	One-eighth atmosphere or 96 mm Hg
100,000 feet	One-ninety fifth atmosphere or 8 0 mm Hg
150,000 feet	One-seven-hundredths atmosphere or 1.08 mm Hg

The composition of dry air is quite constant up to about 50,000 feet with about 21 per cent oxygen, 78 per cent nitrogen and a fraction of a per cent made up of rare gases At about this altitude, part of the oxygen is transformed into ozone, primarily by photochemical processes from the solar radiation. The interaction of cosmic rays may also play some part in this The concentration of ozone reaches toxic levels at about 60,000 feet and its highest concentration at around 70,000 feet [21] At extreme altitudes, the little oxygen present is in the ionized form Nitrogen and its compounds are now believed to play very important photochemical roles above 75 miles Much research is in progress studying the photochemical and other processes taking place in the upper reaches of the atmosphere by the use of rockets and balloons, together with increasingly precise instrumentation [17] The interactions of radiation from the sun and cosmic sources with the constituents of the atmosphere at extreme altitudes is only now beginning to be understood

The physiologic effects of flight are closely related to the effects described by the laws governing gases

Boyle's Law The volume of a gas is inversely proportional to the pressure, provided the temperature is kept constant Common effects in aviation associated with this law come from the result of changes in volume of entrapped gas in the middle ear, sinuses and intestinal tract

Charles's Law The volume of a gas at a constant pressure varies directly with the absolute temperature The aircraft oxygen system pressure drops because of the diminishing temperature as the altitude increases, and oxygen tanks are allowed to cool

Henry's Law The weight of a gas passing into solution varies directly with the partial pressure of that gas Examples of the physiologic effects of this at altitude are seen in the disturbances due to tiny, evolved bubbles containing nitrogen and CO_2 in body tissues at altitudes above 25,000 to 20,000 feet This is called decompression sickness Symptoms are usually referred to as "bends," "chokes," and "creeps"

Dalton's Law When gases or vapors are present in a given space, the pressure exerted by each constituent gas is the same as if its mass filled the entire space alone, thus, the total pressure is equal to the sum of partial pressures due to each gas or vapor It follows that the reduction in barometric pressure encountered in ascent to altitude leads to a loss in the partial pressure of oxygen, which is the key element for energy metabolism in the body

Respiration, which is the exchange of oxygen against carbon dioxide, between the gaseous environment and the living cells is accomplished by ventilation, circulation and diffusion The two former involve mechanical work, namely, the movement of air to and from the lungs and the movement of blood through the vascular system by the heart. Diffusion, which takes place between the lung gases and pulmonary capillary blood, as well as between the peripheral capillary blood and the cells, is the passage of molecules from areas with high partial pressure to regions with lower partial pressure Force and direction of diffusion are determined by the prevailing pressure gradients Under barometric conditions at sea level, ventilation and circulation are able to uphold the pressure gradients necesary for diffusion in the lungs and in the tissues over a wide range of metabolic activity. At altitude, however, the reduced partial pressure of oxygen imposes serious limitations on respiration by curtailing the over-all pressure head for diffusion to the tissues It must also be considered that the partial pressure of oxygen in the lungs is lower than in the environment due to the pressure of water vapor and carbon dioxide The water vapor exerts a pressure of 47 mm Hg at body temperature, regardless of the barometric pressure, so that on ascent to altitude it represents an increasing fraction of total pressure At 63,000 feet, where the barometric pressure is at 47 mm Hg, there is virtually no room for oxygen or any other gas in the lungs The carbon dioxide pressure is governed by the production of this gas in metabolism on the one hand, and the rate of pulmonary ventilation on the other Since the body ordinarily responds to altitude by a moderate increase in ventilation, the carbon dioxide pressure tends to fall with a corresponding gain in oxygen pressure These circumstances are represented in FIGURE 5, where the inspired or tracheal oxygen pressure (interrupted lines), and the alveolar oxygen pressure (solid lines) at altitudes up to 22,000 feet breathing air, and to 46,000 feet breathing oxygen are plotted as far as actual measurements have been made in man during gradual ascent The shaded

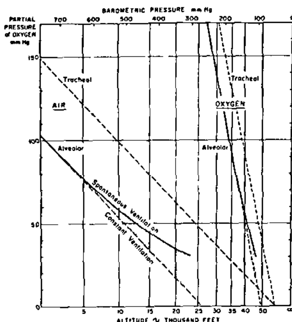


FIG 5—Partial pressure of oxygen at altitude in the inspired (tracheal) and alveolar gas when breathing air (left) and oxygen (right) The constant ventilation line designates course assuming no spontaneous increase in ventilation at altitude (Reprinted through courtesy of the publisher[3])

areas indicate the oxygen pressure gained by the spontaneous increase in ventilation By comparing points with the same tracheal oxygen pressure (*interrupted lines*), locating air (*left*) and oxygen (*right*), it is possible to establish physiologically equivalent altitudes For instance, breathing air at 10,000 feet is equivalent to breathing pure oxygen at 39,000 feet In both instances, the tracheal oxygen pressure is close to 100 mm Hg In gradual ascent at a rate of 1,000 to 2,000 feet per minute, critical signs of altitude sickness immediately preceding unconsciousness occur at 22,000 to 23,000 feet in healthy young adults where the alveolar oxygen pressure drops below 30 mm Hg By displacing the nitrogen from the inspired air with increasing concentrations of oxygen in order to ensure the necessary oxygen pressure, sea level equivalent conditions can be maintained up to about 33,000 feet At this altitude, pure oxygen still provides a normal alveolar oxygen pressure. If ascent is continued, however, altitude sickness inevitably supervenes, and critical symptoms are again encountered at 45,000 to 46,000

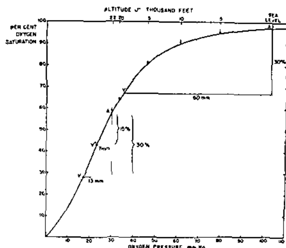


Fig 6—The oxygen dissociation curve with average arterial oxygen pressures at sea level and at altitudes up to 22,000 ft (Reprinted through courtesy of the publisher[2])

feet A small additional advantage can be gained by the use of pressure breathing, which raises the pressure in the airways and lungs, and thus improves the oxygenation of the blood With special equipment of this kind, it is possible to survive at 50,000 feet in emergencies for a limited period At altitudes above 50,000 feet, life cannot be sustained without an artificial pressure environment with a minimum 3 psi (155 mm Hg) of pure oxygen This can be accomplished either by wearing a pressure garment or by enclosing the aviators in a pressurized compartment In civil aviation, cabins pressurized to an equivalent of 6,000 to 8,000 feet, regardless of operational altitude permit passengers and crew to breathe air throughout.

The human organism possesses a number of highly effective means of safeguarding the actual supply of oxygen to the cells One of these, the increase in pulmonary ventilation, has already been mentioned Another is the peculiar manner in which oxygen is transported by the blood, or more precisely, in the hemoglobin of the red cells While only a small amount of oxygen is carried in physical solution in the plasma, about 100 times more is carried in reversible binding with hemoglobin when fully saturated. Figure 6 shows the relationship between oxygen pressure and saturation of the blood in a dissociation curve onto which are projected the average oxygen pressures at different altitudes On ascent to 10,000 feet the pressure drops from 100 to above 60 mm. Hg, but the saturation is still 90 per cent With increasing altitude, however, where gas exchange takes place on the steep part of the curve, arterial oxygen saturation diminishes more rapidly On the other hand, the pressure loss for a given oxygen utilization is smaller. The characteristic configuration of the oxygen dissociation curve accounts for the relatively mild disturbances at altitudes below 10,000 to 12,000 feet, and the marked deterioration at higher altitudes

The rise in heart rate, invariably present in acute exposure to altitude, reflects an increase in cardiac output and peripheral blood flow In consequence of this, the blood is deprived of less oxygen and its passage through the tissues for a given oxygen consumption, and a higher oxygen pressure is maintained at the cellular level and in the mixed venous blood This is indicated for an altitude of 22,000 feet in Figure 6, where the oxygen utilization of the blood between the arterial point A′ and the venous point V″ is only 15 per cent, where the cardiac output is doubled, instead of 30 per cent without changes in cardiac activity

The efficacy of the mechanisms of adaptation to altitude on acute exposure is best revealed by comparing the changes in oxygen pressure in the capillaries at the tissue level with the corresponding changes in the environment In Figure 7, the total oxygen pressure gradient is presented in the form of a series of cascades between the dry atmospheric air and the venous blood as it leaves the systemic capillaries In contrast to the considerable reduction in oxygen pressure in the atmosphere at 10,000 feet and even more so at 20,000 feet, the loss in effective diffusion pressure in the systemic capillaries is relatively small The gradient between alveolar air and arterial blood is diminished due to increased ventilation, while both the character of the oxygen dissociation curve and the increase in blood flow account for the small arteriovenous pressure difference at altitude.

Nevertheless, the scope of physiologic adjustments, particularly in acute exposure, is

limited and with increasing altitude the oxygen utilization of the tissues inevitably suffers Inefficiency of aerobic metabolism or hypoxidosis*[31] is commonly present in a wide variety of pathologic conditions at sea level This may be due to hypoxemia in respiratory or cardiovascular inefficiency, or to reduced oxygen capacity of the blood, as in anemia and carbon monoxide poisoning. Similarly, a lack of fuel for oxidation, for instance, in hypoglycemia may interfere with metabolism in the presence of abundant oxygen Finally, inhibition of oxidative enzymes by cyanide or other agents can cause hypoxidosis Any person in whom even mild hypoxidosis exists under normal barometric pressure will obviously be more susceptible to the effects of altitude, a fact which deserves careful consideration by physicians concerned with aviation

Beyond doubt hypoxia is the most dangerous stress condition occurring at altitude In a larger sense, this is equally true wherever it may be encountered in patients in the practice of medicine and surgery. Hypoxia tends to be insidious and treacherous in its onset and effects in that the dulling of mental processes usually robs the subject of the awareness of danger, even in the face of obviously impending disaster. If permitted to become severe or prolonged, death may follow without evident symptoms of serious distress Thus, hypoxia, which usually appears as a terminal phenomenon, may be considered as the merciful gift which eases the pain of death itself. Every effort should be made to prevent either circumstances leading to hypoxia, or to provide quickly an adequate supply of oxygen at the earliest possible moment.

The brain, which represents about one-fiftieth of the body mass, utilizes on the average about one-fourth of the total blood circulation It is the most susceptible organ to oxygen lack, or decreased oxygen availability from whatever cause, and this is manifested by early and surprisingly rapid deterioration in cerebral efficiency The extent of this parallels the severity of oxygen deprivation It is considered that even relatively short exposure to oxygen deprivation may cause the death of some brain cells Long exposures of some severity are commonly followed by evidence of mental deterioration Prolonged severe hypoxia may be followed by complete loss of the cerebral function even though the rest of the body might survive. Examples of this may be seen in severe barbiturate poisoning with respiratory arrest, followed by later resuscitation

* Defined in reference 31 Oxygen want or deficiency; any state wherein a physiologically inadequate amount of oxygen is available

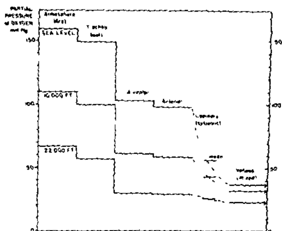


FIG 7—The total oxygen pressure gradient presented in a series of cascades between the dry atmospheric air and the venous blood as it leaves the systemic capillaries

There is a rather wide range of individual variation in symptoms of hypoxia so that military flight surgeons have long recommended runs in a low-pressure chamber at regular intervals for jet pilots and aircraft crews who will fly at the higher altitudes This assists in their understanding and appreciation of the earliest symptoms of hypoxia as well as the insidiousness of the danger. Air crews for jet airliners should also have this type of training There is some slight day-to-day variation in susceptibility to hypoxia in the same individual, depending on the amount of smoking, fatigue, degree of activity, emotional state and other factors.

It is known that a certain amount of acclimatization to altitudes takes place among people who live at the higher altitudes. However, this does not occur appreciably as a result of exposures to 10,000 to 15,000 feet for relatively short periods as in flying, but usu-

ally requires weeks of continuous living at these altitudes The most remarkable example of acclimatization is seen among the Indians working in the tin, silver and copper mines in the Andes Mountains of South America [6] Here people work, live and even engage in active sports at 15,000 to 17,000 feet By contrast, as noted below, most individuals brought rapidly to this altitude are severely impaired Members of mountain climbing expeditions, such as those to Mt Everest in Tibet, must strenuously train themselves over many weeks. They may likewise develop similar acclimatization, though only exceptional individuals appear to be able to do so to this extent.

Severity of symptoms of hypoxia depend on the altitude and somewhat on the rate of ascent These symptoms become more severe as the duration of exposure increases Lower ambient temperature and increasing physical activity both usually accentuate the effect of hypoxia. Poor physical fitness, age, overweight, excesses of smoking play a similar though somewhat lesser role The more severe or prolonged hypoxia exists, the longer the recovery period from symptoms, such as headache, depression, exhaustion and nausea

The onset of hypoxic symptoms in ascent to altitude at a rate of 1,000 to 2,000 feet per minute in normal, young adult, unacclimated individuals is summarized as follows:

0 to 5,000 feet	Normal, no symptoms
5,000 to 8,000 feet	No symptoms while resting, night vision may be impaired, increased breathlessness on exercise
3,000 to 10,000 feet	Fatigue, insomnia, irritability, definite breathlessness on exertion, headaches, if exposure is prolonged
10,000 to 15,000 feet	Insidious, progressive mental deterioration, impaired judgment, becoming marked, poor discrimination, definite slowing of reaction time, with frequent errors, visual changes, headaches, and occasionally exhilaration, extreme breathlessness on exertion with rapid increase in severity of symptoms; abdominal distention may be noted, becoming more prominent at higher altitude unless relieved, rapid pulse
15,000 to 22,000 feet	Decided accentuation of above symptoms with cyanosis, weakness, tremors of extremities, breathlessness, unconsciousness *usually occurs in 10 to 30 minutes*, often without warning of danger to the individual, and death may occur if exposure continues several hours
22,000 to 25,000 feet	Loss of useful consciousness in 4 to 7 minutes as a rule, preceded by profound impairment This is the altitude at which death may occur after relatively short exposure of *less than 30 minutes*

Since at the present time flights above 10,000 feet are invariably undertaken either with oxygen equipment or in pressure cabins, acute hypoxia is encountered primarily in emergencies due to interruption of oxygen supply, or failure of cabin pressure at altitudes well above the physiologic ceiling of the occupants FIGURE 8 shows the average time of useful consciousness in healthy young men after removal of their oxygen masks at altitudes below 22,000 feet and 40,000 feet (*interrupted line*) In rapid decompression without oxygen, the course of events is even more precipitous This is due to the fact that the alveolar oxygen pressure drops simultaneously with the cabin pressure, regardless of respiratory movements, whereas at least several breaths are required to dilute the oxygen in the lungs after cutting off the oxygen supply

Rapid decompression in flight above 50,000 feet brings unconsciousness in 10 to 15 seconds, regardless of whether the occupants are breathing air or oxygen in the cabin, and the chances of survival are slim indeed, unless pressure suits are worn

As can be noted, the most profound effects are on the brain As will be *mentioned in detail* later, older individuals with arteriosclerosis and the infirmities of age, those with coronary disease, anemia and pulmonary insufficiency show the same symptoms of hypoxia

but these occur more rapidly and at a lower altitude, depending on the severity of their individual pathologic processes

The special senses are affected quite early in *hypoxia*. There is impaired vision with eye muscle imbalances becoming more prominent Actual diplopia may occur, accommodation is diminished, and touch and pain senses are impaired. Hearing, although decreased, appears to be the most stable special sense and is usually the last to disappear. As mentioned previously, mental processes are affected early and are usually profound. Judgment is poor, thinking is slow and inaccurate, and reaction time becomes very long If the hypoxia is sufficiently profound, no response occurs at all, even to obviously serious situations. Personality changes are common The emotional patterns frequently are somewhat similar to those seen in alcohol intoxication, including elation and euphoria or depression which may persist until collapse Muscular co-ordination diminishes quite early and becomes severely impaired as hypoxia increases Stammering and illegible handwriting are common examples

By providing sufficient oxygen (promptly) to those with hypoxia, there usually is rapid recovery of full consciousness, often in no more than 15 to 30 seconds. Occasionally, hypoxia to the point of unconsciousness or near unconsciousness is followed after recovery by confusion and agitation for a brief period Occasionally, this may require mild restraint and temporary assistance There may also be depression, lassitude, headaches and nausea lasting for a day or two, particularly if the hypoxia has been moderately severe or has persisted for more than a few minutes

The manifestations of hypoxia are inseparable *from* those of hypocapnia which invariably develops during acute exposure to altitude This is due to the elimination of more carbon dioxide by the lungs than is being produced in metabolism in the course of hyperventilation *stimulated* by hypoxia Excessive loss of carbon dioxide from the blood shifts the acid-base balance toward alkalosis. Severe hypocapnia in itself can produce dizziness, confusion and other cerebral symptoms which are indistinguishable from hypoxia Thus, voluntary or

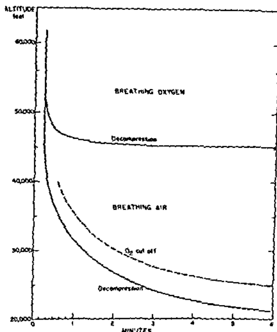


FIG 8—Solid curves time of useful consciousness at altitude after rapid decompression breathing air (*below*) and breathing oxygen (*above*) in pressure cabin Interrupted curve time of useful consciousness after separation from oxygen supply in unpressurized cabin

spontaneous excessive hyperventilation caused by anxiety or faulty oxygen equipment may give rise to serious impairment even in the presence of adequate oxygen supply.

Another effect of exposure to altitude in normal individuals is decompression sickness or dysbarism *[13] It is the result of the difference between the barometric pressure and the pressure of trapped gases in the body cavities or dissolved in the body fluids There are two types of dysbarism [13] One perhaps more commonly seen below 25,000 feet is simply due to the expansion of entrapped gas or air in hollow organs, and the other usually seen above 25,000 to 30,000 feet is the result of tiny bubbles of nitrogen and CO_2 being evolved from the blood and tissues

A common example of the first type which is due to trapped air in hollow organs is the abdominal distress which develops as a result of the expansion of gas in the stomach and in-

* A condition of the *body* resulting from the existence of a pressure differential between the total ambient barometric pressure and the total pressures of *dissolved* and free gases within the body tissues, fluids and cavities

testinal tract from diminishing atmospheric pressure as altitude increases This follows Boyle's Law and is often first observed between 15,000 to 25,000 feet altitude where moderate discomfort or mild pain is noted As a rule, there is no discomfort until expansion increases to about twice the previous volume As *one ascends to about 35,000 or 40,000 feet*, for example, this gas expands to something over five times the sea level volume and marked pain may result It is relieved by eructation or the passing of flatus

Similarly, the small volumes of air en*trapped in the middle* ear cause discomfort more commonly and more rapidly than perhaps elsewhere in the body During ascent, at about 500 to 1,000 foot intervals, most individuals feel a sense of pressure or fullness in the middle ear This is usually relieved by the spontaneous opening of the eustachian tube, which allows the air to escape, thereby equalizing the pressure Individuals may notice a click, followed by a distinct change in the quality of hearing Pain in the ear occurs when a pressure differential of about 30 mm Hg builds up across the tympanic membrane causing it to stretch Rupture of the tympanic membrane will occur between 100 and 500 mm Hg difference in pressure, particularly if the decompression is extremely rapid and if there is obstruction of the eustachian tube orifice

With descent, air must enter through the eustachian tube to the middle ear to equalize again the pressure on both sides of the tympanic membrane This is usually accomplished by swallowing or yawning, and is followed by *changes in the quality of hearing In babies* aboard unpressurized aircraft, this discomfort often causes them to cry, and this act will of itself usually cause the eustachian orifice to open. Individuals with acute coryza or obstructive processes in the eustachian tube or *its orifice may* experience severe discomfort, and, in extreme cases, damage to the tympanic membrane may result Ordinarily, these pressure inequalities may be relieved by holding the nose and mouth tightly closed and forcibly exhaling, thereby raising the air pressure in *the nasopharynx* to the point air passes up the eustachian tube to the middle ear. Dramatic *relief of discomfort or pain usually follows*, and hearing returns to normal. In extreme cases, an otolaryngologist can insufflate the eustachian tube under direct vision using a nasopharyngoscope and a eustachian catheter. These disturbances in equalization of air pressure in the middle ear, if prolonged, give rise to a condition called aerotitis, or barotitis.* This condition has become much less common as pressurized cockpits and pressurized aircraft have come into more general use A similar condition may develop in connection with the paranasal sinuses with changes in atmospheric pressure Occasionally, in teeth, usually with defective fillings, gas expansion with altitude causes pain.

A curious type of aerotitis is recognized in military pilots flying high-performance aircraft using oxygen masks in partially pressurized cockpits of jet fighter aircraft Here, when flying at great altitudes, they are breathing 100 per cent oxygen During flight, the proportion of oxygen in the few centimeters of air in the middle ear and mastoid cells connected therewith gradually increases. *Also*, during descent, pure oxygen passes up the eustachian tube, still further increasing the proportion of oxygen Thus, on reaching ground level at the termination of flight, there is no noticeable difference in pressure on the *two sides of the tympanic membrane* However, during the next few hours because of the very high partial pressure of oxygen, the capillaries in the wall of the middle ear and mastoid cells gradually absorb the oxygen, thereby diminishing the pressure in the middle ear This is generally relieved by swallowing or yawning from time to time in the usual way, so that after some hours the relative proportion of the gases returns to normal Should this occur at night, however, and the pilot falls asleep before the gas mixture returns to nearly normal proportions, he may awaken some hours later with acute aerotitis The middle ear will then often become partially filled with a serous exudate. This usually absorbs after a few days Aerotitis, particularly if re-

* Inflammation of the ear, or a part thereof, caused by changes in atmospheric pressure

peated, can result in permanent changes in the ear structure, diminished hearing, tinnitus and occasionally impaired equilibration In order to diminish this and to prevent sinus disturbances from the same causes, cabin pressure changes in commercial transport aircraft are usually limited to about 0 1 pounds per square inch per minute. In the new commercial jet aircraft, it is possible to maintain sea level pressure up to (approximately) 25,000 feet The cabin pressure will not drop below 5,000 to 8,000 foot pressure equivalent, even at the greatest altitude they expected during the flight

In addition to hypoxia and the effect of changing volumes of entrapped gases in the body cavities as a result of decreasing atmospheric pressure, the second type of decompression sickness may become troublesome on exposing individuals to pressure equivalents of 25,000 to 30,000 feet or more This type of decompression sickness is caused by the evolution of tiny bubbles of nitrogen and CO_2 in the spinal fluid, blood and tissues The symptoms are variable in their onset and severity depending on individual susceptibility and the rate of decompression or ascent and the location of these bubbles in the body structures

"Compressed air illness" was first associated with diving operations or work inside of caissons and resulted from the too rapid diminution of the increased air pressure under which the individuals were working Because of the wide range of variation in sypmtoms, decompression sickness has been given a number of descriptive names by these workers including bends, caisson disease, chokes, creeps, itch, staggers, diver's palsy and paralysis This interesting subject is discussed in detail in Chapter 62 It had long been known empirically that it was good practice to diminish the pressure by not more than half at one time and to allow a waiting period between stages of decompression of about 30 minutes per atmosphere to allow the excess nitrogen to escape Decompressions more rapid than this cause bubbles of nitrogen and CO_2 to evolve in the blood and tissues giving rise to the variety of symptoms cited above It remained for Armstrong[2] to show that similarly rapid reduction of pressure from one atmosphere to less than one-half atmosphere also produced an evolution of nitrogen bubbles in the blood and tissues giving rise to identical symptoms in flyers, as previously noted in divers after too rapid decompression from higher pressure (toward atmospheric pressure) He called this aeroembolism

At sea level pressure 1 5 cc nitrogen is dissolved in 100 cc blood at body temperature The tissues of the body are normally saturated with nitrogen from the atmosphere As one gains altitude and as the pressure diminishes, the nitrogen in the tissues and blood becomes over-saturated The excess nitrogen dissolved in the blood passes into the alveolar air and is exhaled Oversaturated nitrogen from the tissue passes into the blood and is also gradually lost if sufficient time elapses and the altitude is not excessively high In obese individuals this takes longer, because fat absorbs about five or six times as much nitrogen as other tissues Thus, as one is subjected to diminishing atmospheric pressure, dissolved nitrogen is lost first from the blood, next from lean body tissues and finally from fat and related substances The first actual appearance of tiny bubbles is usually in the spinal fluid which is not in intimate contact with circulating blood This is occasionally seen in animals at around 18,000 to 20,000 feet ambient pressure The more rapid the loss of pressure, the less chance the body has of ridding itself of excess nitrogen, and so the nitrogen bubbles evolve more quickly and possibly are larger

Dysbarism has long been troublesome to pilots flying military aircraft at high altitudes, largely because the aircraft has not been highly pressurized in order to reduce weight, thereby increasing performance Previously, civilian airliners did not reach altitudes in excess of 18,000 to 20,000 feet, where aeroembolism could be expected, until the recent advent of turbo-jet airliners Among these are the Boeing 707, the Convair 880 and the Douglas DC-8 in the United States Several years previously, the English Comet and later the Russian jet airliners also reached these altitudes

The symptoms of aeroembolism are extremely variable because they depend on the

development of tiny bubbles, notably their location and size in the body. The bubbles in the tissues cause pain, principally in relatively unyielding structures, e g , bone, tendons, fascia and nerve sheaths Central nervous system disturbances occur, depending on the size and location of bubbles and consequent interference with cerebral function or nerve conduction The blood stream, however, is probably the most frequent and dangerous point of involvement because of the development of embolic phenomena, which in turn cause symptoms depending on their location

In the bones and joints, pain, occasionally unbearable, occurs in the knee, finger, shoulder, ankle and hip joint and in about this relative order of frequency These were called "bends" in years past In the skin, a burning sensation, formication, itching, neurodermatitis and even large, urticarial wheals can occur This group of skin symptoms was called the "creeps" by the divers and caisson workers In the nervous system, neuritis, paralysis, convulsions and neurocirculatory collapse occur In the respiratory system pain, choking, pulmonary edema and coughing are seen in about this order These respiratory symptoms are called the "chokes" In some cases, death can occur

The above phenomena of hypoxia and decompression sickness (*dysbarism*) can occur in commercial airliners only with loss of cabin pressure. Dysbarism develops only in the extremely unlikely situation in which altitudes are maintained for more than 10 to 15 minutes, even with a loss of cabin pressurization Aircraft design engineers and manufacturers have applied every known safety measure to eliminate this dangerous contingency The source of pressurization in jet airliners is from the compressors in the engines. There is one provided for each of the four engines, all being fully capable of supplying the normal cabin requirements Much attention has been given to the ducts and valves so that "blow-outs" cannot occur. Thus, great care has been given to the reliability of the pressurization sources

The commonest causes of decompression in transport aircraft in the past have been the loss of windows, windshields or hatches Much has been learned from previous failures, to improve design, strength and reliability of such structures. In any event, damage or impairment will not cause explosive decompression, defined as taking place within one-half second. Airliner depressurization accidents, if they occur, will ordinarily result in cabin pressure loss in from 10 to 15 seconds—perhaps as long as one or two minutes or more, if the opening is small Under such circumstances, the rate of pressure loss depends on the size of the opening, the total air volume of the cabin, the pressure differential due to the difference between cabin altitude and true altitude, and the total volume of pressurization air which can be supplied in the emergency by all of the compressors The hypoxic and decompression sickness effect on crew and passengers will depend on the actual altitude of the aircraft, the rate of decompression as well as the total exposure time above critical altitudes This will depend on the time it takes for the pilot to ascertain the difficulty, time to start descent and the rate of descent Rates of descent of from 8,000 to 12,000 feet per minute are possible in modern jet airliners Design engineers and manufacturers have so improved the design and construction of vulnerable points, that likelihood of failure is extremely remote

From past experience in explosive decompressions in military aircraft and low pressure chamber work, the following sequence of events is probable There would be a loud "bang" or report in the vicinity of the defect, followed by the loud rumble and high-pitched blowing sound of escaping air A rapid drop in air temperature would follow because of air expansion This might cause a fogging of the cabin air, especially with humidity, but this will usually clear again after a few seconds The rapid movement of air in the cabin can be expected to pick up loose, light-weight objects and dust In rapid decompressions, the passengers may note a forceful expiration of air from their lungs, a sense of fullness and perhaps pain in middle ears and sinuses while air is escaping from them, as well as a fullness and possibly faintness, chilling and confusion There may be a tendency to panic, which must be avoided. If the passenger is able to don his oxygen mask quickly, as instructed, he will soon feel normal.

The pilot who is required to wear an oxygen mask at all times when flying over 25,000 feet would be expected to start his maximum safe rate of descent within the first one-half minute or so, and should reach a safe altitude within two to four minutes While this is a serious in-flight emergency in aircraft operation, all individuals in reasonable health should have no serious difficulties, providing the crew reacts promptly in bringing the aircraft rapidly to a safe altitude Decompression symptoms are unlikely in this short period of time

During the earliest phases of such a descent, if very rapid, the passengers may notice "diminished" weight or perhaps even weightlessness for a few moments When the lower altitude is reached, they may notice an "increased" weight as the rate of descent of the aircraft is checked and it levels out at the lower safe altitude This variation in apparent "G" or *gravity forces* is an extremely important phenomenon in aviation.

Many individuals tend to believe that one can somehow sense or be aware of speed Actually, even at speeds far in excess of 500 to 600 miles per hour, especially at turbo-jet airliner's cruising altitudes of 30,000 to 40,000 feet, there is little or no sensation of motion This is because clouds and haze below often impair downward visibility, and ground reference points are at considerable distances It is only when the direction of flight is changed that one is made aware of the forces acting on the aircraft and its occupants So long as the aircraft is proceeding along a straight course parallel with the surface of the earth, there is essentially no sense of motion or change in weight Should the aircraft begin an abrupt climb, or a sharp turn, the passenger is forced down in his seat, his weight is apparently increased, and he is said to be subject to positive "G's" Average healthy young adults are able to tolerate from three to five positive "G's" for periods of approximately five seconds or more before noticing their vision becoming dim (grey-out) or disappearing altogether (black-out) Under these conditions, leg and arm movements are difficult or impossible because of their weight, and the neck is often unable to hold the head erect Breathing is often difficult under these conditions Higher "G" forces may lead to unconsciousness or injury

If the pilot starts a sudden dive, the passengers now notice that they are not sitting as firmly in their seats, and are apparently lighter than normal They are now subject to less than one "G" If the dive is suddenly made steeper, the passenger will, unless restrained by the seat belt, be lifted out of his seat and may strike the ceiling of the aircraft If he is restrained by the lap belt, he is said to be exposed to negative "G" He will fall back in his seat when the aircraft levels out It is possible for brief periods of a few seconds only, to cause the aircraft to descend at the same rate a person falls back, and under these conditions, he may be subject to zero "G" or weightlessness It is precisely this phenomenon taking place in a space ship or capsule in orbit which produces weightlessness over indefinite periods for the crew therein. Should the aircraft accelerate rapidly, the passengers are subject to transverse "G", that is, front-to-back Other types of transverse "G" would be back-to-front, as in deceleration, and lateral transverse "G" is experienced, if the aircraft pilot moves the rudders strongly to the right or left Passengers who have ridden in aircraft through severe storms or air turbulence have noted examples of each of the above-mentioned types of "G" forces The generally accepted tolerance limits of "G" forces applied in different directions with respect to the body are shown in FIGURE 9.

In order to permit military fighter pilots to withstand increased "G" forces, "Anti-G" suits have been devised These consist of an inelastic, tight-fitting garment covering the lower half of the body Inside the garment is a bladder which may be filled with air which exerts a counter pressure on the lower extremities and abdominal area in proportion to the "G" forces, preventing the pooling of blood in these areas during positive "G's," thereby maintaining or supporting circulation.

Under conditions of moderate to severe turbulence, motion sickness is frequently experienced by passengers This is particularly true if the turbulent condition persists for more than a few minutes. There is no essential difference

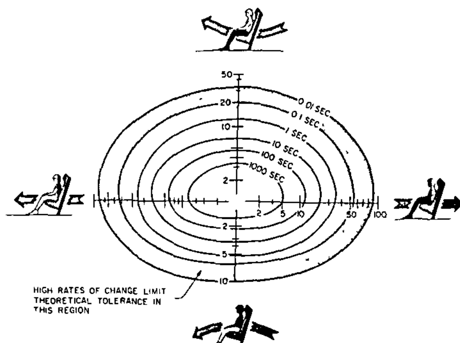


Fig 9—Acceleration tolerance (By permission of A M Mayo, Douglas Aircraft Co, Inc, El Segundo Division)

in the symptoms of motion sickness or in remedies for its relief, as noted in ocean liners or in the air. With jet airliners, the amount of turbulence is considerably less as a rule, because of the fact that the altitudes at which flight is maintained are above all but the most severe weather disturbances, and motion sickness reduced thereby

Heating, cooling and ventilation in passenger aircraft, together with adequate pressurization, are extremely interesting and practical problems It has been determined that because of the relatively high passenger density to cabin volume, about 35 to 40 cubic feet of fresh air per passenger per minute are necessary if irritating concentrations of tobacco smoke and body odors are to be avoided. With good ventilation the likelihood of air sickness is diminished as well In highly pressurized turbo-jet aircraft about 15 to 20 cubic feet of fresh air are provided each passenger, plus 20 cubic feet of odor-free, recirculated air Cabin air velocities of 20 to 60 feet per minute are also provided to give a sense of freshness.

Air at the higher altitudes normally has a very low relative humidity. As noted previously, at 35,000 feet and above, air holds a constant temperature of about 67 degrees below zero Fahrenheit, winter and summer and is somewhat colder over the equator than over polar areas. As this cold air is brought into the aircraft and heated to cabin temperatures, the relative humidity of the cabin air may well approach zero in a nearly empty aircraft

Consequently, a few passengers will complain of nose and throat dryness and, occasionally one may note some bronchial irritation Experience indicates that the relative humidity in a fully loaded turbo-jet transport will be around 5 to 10 per cent when flying at altitude This is actually not far different from that found in many homes during the winter, in the colder parts of the country. Beverages are served to overcome dehydration. Humidification has not been considered essential, and has not been provided in American jet airliners However, the British jet airliners provide humidification

Of great concern in military aircraft in the past, are toxins which can exist in vapor form These include vapor from fuels, hydraulic fluids and fire extinguishants such as carbon tetrachloride. Smokes and other toxic vapors from thermal decomposition of fuels and oils are all potentially dangerous. Carbon monoxide and carbon dioxide are especially dangerous

as their relative effect is increased at altitudes. It may be said in general that the effect of inhalation of toxins will be additive to the effect of hypoxia though the exact relationship is not fully known in all cases. In carbon monoxide poisoning which lowers the oxygen carrying capacity of the hemoglobin, the additive effect to hypoxia is quite marked Even the amount of carbon monoxide absorbed by smoking will lower the altitude tolerance by a thousand feet or more.

Cosmic radiation has recently received considerable attention because it is known to increase in intensity as one reaches higher altitudes At 35,000 to 40,000 feet in the latitude of the United States, this reaches average levels around 6 milliroentgens equivalent per 24 hours of exposure. Solar flares may temporarily increase these values several fold, but they are of short duration It has been estimated that were air crews to fly at altitudes of 50,000 to 60,000 feet for average weekly tours, they may receive an accumulated radiation dosage of 50 roentgens over a 10 year period The biologic effectiveness of this body dose is, of course, reduced by the length of time over which it is attained Another important concept of radiation hazard is that the flight times at speeds to be attained at these altitudes in the future will be much less than now for the same distances, so the net effect of accumulation dose may be no more than at present It may be said with reasonable confidence that cosmic radiation does not offer a noteworthy hazard to passengers or aircrews at altitudes of turbo-jet airliner flights which are below 40,000 feet, and may not become a problem at greater speeds and altitudes

For some years since military aircraft have penetrated the stratosphere for flights of considerable periods, it has been found that fission fragments from thermonuclear or fission weapon tests will gradually become attached to various portions of the aircraft, particularly at points where air turbulence is high The amount and type of this depends mostly on the length of time since the last series of nuclear test shots have taken place anywhere in the northern hemisphere. This radioactive contamination is found mostly in the jet engines on the turbine blades, the air compressor turbines, then the nose and leading edges of the wings and tail surfaces, in this order Extensive study of this phenomenon by the United States Air Force has shown that if the small, barely detectable amounts of radiation found in the cabin and crew compartments are taken as 1, the nose and leading edges of the wings will have approximately 10 times as much, and the turbine blades in the jet engines about 100 times these levels

It should be emphasized that the maximum levels of contamination found are still well below the generally accepted minimum safe levels of exposure for ground crew, service and even overhaul personnel working on the jet engines They are negligible for passengers and air crews For aircraft service and overhaul personnel, the application of normal hygienic practices of washing the hands with soap and water, prior to eating and after work, and the usual routine laundering of work uniforms is considered sufficient to reduce any possible remote hazard to insignificance Because of the very low contamination levels, no decontamination procedures are believed required for equipment handling, even for the highest levels of contamination found in the jet engines in connection with their overhaul or maintenance At the highest levels found in jet aircraft operating at the northern latitudes, where the lower border of the stratosphere is at the lower altitudes, averaging around 30,000 to 35,000 feet, the engines were found to have an average reading of less than 0 030 milliroentgens per hour The level of contamination in passenger and crew compartments was so low as to be barely detectable At the highest readings found, and for engine overhaul personnel, this exposure is less than 40 per cent of the permissible level in unsupervised or uncontrolled areas, according to National Committee on Radiation Protection as described in The National Bureau of Standards Handbook No 52 and addendum This level of exposure gradually diminishes as the time increases since the last test series It is noteworthy that the air compressor turbine blades capture most of the radioactive contamination particles in the volume of air going to the

crew and passenger compartments, thus acting something like a filter in this respect They gradually accumulate levels of contamination similar to that found in jet engines. They are overhauled long before this reaches levels where the material is thrown off from the blades

In the past, one of the characteristics of the environment in the vicinity of any large air base or terminal has been the noise produced by the engines and propellers of departing and arriving aircraft In spite of this known characteristic, many homes have been built in such a way that the once open areas in the vicinity of many airports have gradually been replaced by suburban developments Aircraft noise has therefore become a community problem of some magnitude With the advent of jet aircraft, first in the military services, and more recently by the civilian airlines, many residents who perhaps had become somewhat accustomed to the familiar sound of engine-propeller-driven aircraft, have been disturbed, at least temporarily, by the new and different noises produced by jet aircraft Here, the energy spectrum is shifted to the higher octave bands in frequency Particularly was this true in the vicinity of Air Defense Command Fighter aircraft bases Here, in the very high-performance, fighter-type military aircraft operations, additional fuel is sprayed into the after portion of the large turbo-jet exhaust stack which ignites and produces additional thrust. These are called after-burners and when used, there is added to the already considerable jet noise, an explosive report followed by a markedly increased roar This enables the fighter aircraft to get off of the runway faster and to climb at a much higher rate of speed. These characteristics of higher performance are particularly essential in the Air Defense mission and could well prove of crucial importance to the safety of this nation, should it be attacked. No satisfactory noise suppressers have been developed for after-burner-equipped fighter aircraft, though a great deal of development effort is underway On the other hand, considerable progress has been achieved in reducing the apparent noise of the turbo-jet engine in transport-type aircraft engines without after-burners, partly by devices which raise the frequency of the noise spectrum toward the supersonic regions, or change it to much lower frequencies which are not considered so disturbing One such device is seen on the engines of the Boeing 707 turbo-jet airliner. Other types are seen on the Douglas DC-8, and the Convair 880 Additional progress in this field can be anticipated, though a quiet jet aircraft can probably not be achieved because of the energy levels involved

The most important characteristics of sound are its intensity and frequency, the loudness being a function of its intensity The human ear is capable of sensing a relatively wide range of sound energy. The loudest noises the ear can hear without pain, have about one trillion times the energy of the faintest sound which can be heard by the normal ear For practical purposes, in order to handle this wide range of energy, the unit of sound has been adopted—the decibel, which is abbreviated as db The instrument used is called the sound level meter, and it measures the magnitude of the pressure wave in air that travels outward from the source of sound.

The number of decibels determining the ratio of any two sound pressures is defined as:

$$\text{Sound Pressure Level (db)} = 20 \log_{10} (P_1/P_0)$$

The reference P_0 is 0 0002 dynes/cm^2 (0002 microbar) This corresponds to the average threshold of hearing at 1,000 cycles per second It is important that decibels are not added directly An increase of three decibels indicates a doubling of the sound intensity For example, if there are two noise sources, each with an intensity of 100 db, when they are both producing sound at the same time, the total output is 103 db, instead of 200 db

Frequency is the other most important factor in sound measurement, and in effect on hearing The human ear is nonlinear in its response to sound of different frequencies Intensity-wise, the ear is most sensitive to sounds in the 1,000 to 3,000 cps frequencies and becomes somewhat less sensitive to higher and lower frequencies

Sounds of different types which have the

same decibel level can have different human responses Shrill or high-pitched sounds are considered more disturbing than low-pitched rumbling sounds of the same sound pressure reading Because of this, sounds are often electronically analyzed into frequency bands, and the relative proportion of sound in each frequency band is measured This has given rise to the concept of perceived noise level (Pdb).[4]

In addition to all the effects of increasing altitude on the physiology of the unprotected individuals previously mentioned, is the increase in light intensity and glare This is due to the diminishing amount of haze, smoke and dust particles which filter out some of the light at lower altitude. As a result, the sunlight becomes more intense with increasing altitude. The intensity of ultraviolet light also increases with altitude At extreme altitudes, the virtual absence of dust particles in the air reduces reflectance, and the blue sky becomes darker, though this is not very noticeable below about 60,000 feet During the daytime when flying above the clouds, which may extend to 30,000 feet or more, the light may reach intensities that shielding of the eyes with protective lenses is desirable, if not essential for most individuals. Cockpit visibility can then become a problem because of the contrast of light intensities so that strong instrument lighting is desirable This becomes still more of a problem in space vehicles

At economical jet altitudes, from 30,000 to 40,000 feet, pilots tend to fly more and more by instruments making use of radio beams and other electronic navigation aids This requires the attention of the pilot to the instrumentation inside the cockpit for a significant part of the time When he looks outside to scan the sky for other aircraft, his vision may be momentarily impaired because of the extreme brightness outside In addition, because of the lack of any points of reference to stimulate accommodation change, there is a tendency for the eyes to remain accommodated for approximately the instrument panel distance and so become relatively myopic for distance Small, distant objects may therefore not be immediately visible This condition has been called "altitude myopia" Altitude myopia plus the high speeds attained, together with human reaction time thus have important aspects in flight safety, if midair collisions at great altitude are to be avoided

The following table shows the factors which make up the series of actions involved in avoidance of collision The times given are approximate They can be somewhat shorter, but are more apt to be longer for most pilots

1. If the pilot is looking at his instruments and then looks outside he will require 5 to 1 5 seconds to light adapt and accommodate This period increases with age and approaches twice these values on the average at 50 years An average value is 1 0 sec

2 Perception of aircraft	0 1 sec
3 Recognition of aircraft	1 0 sec
4 Awareness of possible collision course	5 0 sec.
5 Decision how to alter course	4 0 sec
6 Muscular reaction	0 4 sec
7 Aircraft lag time	3 0 sec.
	14 5 sec

This is about one-quarter minute At 600 miles per hour, the aircraft flies 10 miles per minute, or 2½ miles in one-quarter minute. This means that if the two aircraft are actually on a collision course, the pilots should perceive each other at least five miles apart, and take immediate evasive action Aircraft 5 miles distant are very easily overlooked at high altitude This illustrates the need for greatly improved air traffic control to supplement the limitations of human perception and reaction

The remaining portion of this chapter is devoted to a discussion of various pathologic conditions involving potential passengers on airliners based on experience to date

Before considering any specific conditions, however, it may be well to discuss some features in airplanes, airplane travel or symptoms that may affect decisions concerning potential passengers In wartime, transportation of patients is a major activity of the military medical departments and the Air Force In peacetime, the transportation of patients, or the public, often becomes a problem in medical practice In the civilian population, the necessity to transport patients frequently requires special attention by the attending physician, or a patient may ask his physician whether or not it is safe for him to travel.

Within the United States, in which medical facilities are usually readily available, severely ill patients rarely need to travel by air. However, some airlines serving cities with large medical clinics do make special provisions for the carrying of patients, even though the facilities of an airline may not lend themselves to sending a specific patient by commercial plane, airplane ambulance services are available throughout the United States These ambulances *are completely equipped, including* adequate oxygen supplies. In addition to space for a nurse, accommodations are also provided for a physician to accompany the patient when necessary

Different airlines have special regulations and rules for the handling of patients These rules cover such items as. method of loading and unloading, provisions for care on board, use of accompanying attendants, etc Since these rules vary from company to company, in specific instances it is wise to consult with the medical departments of the airline They are experienced in these problems and frequently can make suggestions to simplify the transportation of the sick This is particularly advisable in the unusual or the more seriously sick patients.

Contrary to some opinions, sea level altitudes *are not maintained constantly Usually,* there is partial pressurization and the cabin altitude in flight will be above sea level but below the cruising altitude of the airplane This altitude will depend on the degree of pressure differential for the particular type of plane The following chart gives examples of variation of pressure differentials and cabin altitudes for comparison:

Plane	Pressure Differential	Plane Altitude	Cabin Altitude
DC-6 (Douglas)	4 16 psi	10,000 ft 20,000 ft	Sea level 8,000 ft
DC-7 (Douglas)	5 46 psi	12,500 ft 25,000 ft	Sea level 8,000 ft
Electra (Lockheed)	6 55 psi	15,450 ft 30,000 ft	Sea level 8,000 ft
707 (Boeing)	8 60 psi	22,500 ft. 40,000 ft	Sea Level 7,200 ft

The physician should be aware of this varying pressure differential in deciding whether or not patients with anemias, coronary disease or lung pathology should travel by air.[12, 18, 19, 28, 29]

In addition to pressurization, the subject of oxygen should be clarified The federal government requires that oxygen be carried on board any aircraft that flies above 8,000 feet, regardless of whether or not it is pressurized The *amount of oxygen required is for emergency* use, and is adequate for the purpose, but may be insufficient in quantity to maintain an adequate therapeutic rate of flow for an appreciable period of time and still provide sufficient amounts for emergency use Thus, a tank of oxygen, reduction valve and a mask should be rented from a medical supply house, if required in flight by a patient This assures the patient an adequate supply of oxygen for his individual use Many such supply houses have equipment for this purpose

Certain symptoms or signs are found in many diseases which will affect the decision as to whether a patient is medically able to fly or not They also may play a part in deciding whether a commercial plane or an air ambulance is preferable, or if certain precautions should be taken prior to beginning the flight *In all questionable instances, the risks* inherent in flying must be weighed against the advantages to be gained thereby Very few diseases are a contraindication to transportation by air, if the patient can *be moved at all.*

Sometimes the reason for recommending against flying may be due to problems inherent in commercial aviation rather than the disease itself being the restricting factor *For example,* odors may be offensive to other passengers, or splints or other equipment necessary for the trip may not be used easily in a passenger plane In such cases, private *or ambulance* planes should be considered.

Modern planes with superior pressurization equipment, supplemental oxygen and a marked reduction in travel time now make *it easily possible for many patients to fly* (those were formerly otherwise advised). All airline physicians receive frequent requests for assistance in deciding on the transportability of patients Following are some general considerations that

may be helpful to the physician in assisting him in advising the patient:

1 The necessity for the trip. If an illness is temporary, it might be advisable to postpone the trip until the patient has recovered The more serious the pathologic condition, the more urgent must be the reason for considering air transportation, or any other type of transportation

2 Disturbing other passengers Most passengers are healthy and are traveling for business or pleasure It is possible that a passenger with an illness may be disturbing to the other passengers, because the limited space eliminates any degree of privacy for the patient, thus becoming a source of embarrassment both to the patient and other passengers

3 Pressurization There are some planes still in commercial operation which are not pressurized This should be determined prior to flight

4 Enplaning and deplaning The decision must be made as to whether the patient may walk up the steps to the plane or should be carried Will it be necessary to have an ambulance or a wheel chair at the end of the trip? If so, special arrangements must be made beforehand at each point of change of planes

5 Extra supply of oxygen If the passenger will require oxygen for the entire trip, individual tanks should be rented

6 Need for attendant or companion They should be provided for patients who are unable to care for themselves

7 Itinerary If possible, it would be preferable to schedule patients on flights which make few or no stops enroute

Diseases of the Heart[11, 18, 19, 28]

The most prominent diseases of the heart, in respect to air travel, are coronary artery disease (insufficiency), angina pectoris or myocardial infarction These conditions are associated with varying degrees of hypoxia of the myocardial tissues A reduced oxygen intake due to flying, if marked, may produce further damage to the myocardium However, actual experience in air travel with selected cardiac patients has been excellent

Patients with angina pectoris are acceptable for flight if the attacks are not present at rest However, if an attack is precipitated by slight exertion, the individual should not be favorably considered, except under the most urgent circumstances. In the event an attack should occur on an airplane, cabin attendants will provide oxygen, but it should be remembered that this is supplemental in quantity rather than therapeutic. When absolutely necessary, active cases may be transported in ambulance planes with proper facilities, such as therapeutic oxygen, drugs and a physican or nurse in attendance *Patients with anginal symptoms* should, of course, carry nitroglycerine at all times for use during acute attacks

Passengers with myocardial infarction may fly if the attack is more than six weeks past. Some physicians prefer longer periods extending up to six months, depending on the individual (The electrocardiogram must be stabilized) The patient should be free from pain, cyanosis and dyspnea, and should be at the stage in which mild exercise is permitted

Patients with valvular heart disease may be acceptable Obviously, such patients should not be accepted if active rheumatic fever or bacterial endocarditis is present However, if the disease is quiescent, there is no cyanosis, dyspnea or other evidence of left or right-sided heart failure, no difficulty should be experienced in flying In rheumatic heart disease, cardiac insufficiency may be present for many years. In such cases, additional oxygen may make it possible for the patient to travel by air for short periods of time With jet transports, this markedly increases the possibilities for air travel

Hypertensive cardiovascular disease per se is not a contraindication to flying

Congenital Heart Disease[3, 8, 11, 14, 18]

Formerly, very little was or could be done for the patient with congenital heart disease In recent years, this has radically changed, due to improved diagnostic technics Furthermore, the advances in cardiac surgery at various centers have made available treatments never before possible. (Most patients without symptoms may fly without difficulty.) Those with low cardiac reserve, showing cyanosis or dyspnea at rest, or with slight exercise, should have oxygen made available if the trip is essential If the patient is ambulatory and permitted to climb one flight of stairs, the use of commercial pressurized airplanes is not contraindicated If more seriously impaired, each patient should be considered individually, primarily to determine whether additional attendants, or equipment are required for the trip

Cardiac Arrhythmia

Individuals with occasional extrasystoles present no problem Paroxysmal supraventricular tachycardias in the absence of organic heart disease present little difficulty unless the amount of dyspnea is excessive. In such a case, if it is necessary to fly, oxygen should be administered *Atrial flutter is more disturbing* than the tachycardia and the physician should consider the necessity for the trip, and make an evaluation of the cardiac function Cases of atrial fibrillation should be evaluated on the basis of the underlying cause and the need for travel, 100 per cent oxygen and pressurized planes should be used, if it is necessary to make the trip If it is absolutely necessary to fly, proper digitalization beforehand should be considered

Heart Block

Consideration must be given to the etiologic factor and the evaluation of the cardiac function Experience indicates that patients with atrioventricular block and bundle-branch block fly without any difficulty Complete heart block (Stokes-Adams syndrome) is generally a contraindication to flying Wolff-Parkinson-White syndrome is no contraindication to flying

Bronchopulmonary diseases[6, 8, 10, 12, 28]

If pulmonary pathology seriously reduces pulmonary reserve, flights may be hazardous Such cases usually require critical evaluation, the assurance of an adequate supply of oxygen, and the presence of nursing attendants as well as a *satisfactory flight schedule*

Asthma

Passengers suffering from asthma may travel by air between attacks They should have proper medication to control attacks, should they occur.

Bronchitis

Bronchitis is not problem as a rule if not severe, except in older patients where it is a part of another process such as bronchiectasis. Here, adequate medication to control undue coughing should be provided.

Pneumonia

Patients with acute pneumonias obviously should preferably be considered for hospitalization or local care without transporation. If the pulmonary reserve is affected, such patients should not fly. If the patient is comfortable at rest, he can be flown in pressurized *planes with an adequate oxygen supply. Under* emergency circumstances in undeveloped areas in which airlift is the only way to hospitalization, adequate oxygen and proper medication should be used

Emphysema

Emphysema patients do poorly as air passengers as a rule, especially if advanced They are often suffering mild degree of hypoxia at sea level, and even moderate increases in hypoxia are contraindicated In addition, the presence of mild or severe obstructive impairment and air trapping in the lungs increases the risks, should decompression occur

Oxygen Toxicity

Oxygen toxicity which can occur with prolonged breathing of pure oxygen near sea level presents very little problem in emphysema cases This is true because the oxygen supplied in the plane is only present in sufficient quantity and flow rate to approximate sea level conditions The mask used for passengers is one which mixes the oxygen with ambient air Oxygen toxicity in any case is not a problem, unless breathed at sea level altitudes for a number of hours by individuals with normal pulmonary function.

Tuberculosis

Patients with active tuberculosis usually should not be flown, since it is a communicable disease and thus prohibited by public health regulation Those with arrested, uncomplicated disease should present no problem Gas present in any enclosed cavity will expand at altitude, and will compress lung tissue and decrease function Patients with pneumothorax should not fly because of the pressure change. However, it may be possible for one with a therapeutic pneumothorax to fly, if he is in need of a refill The patient who recently has

received a refill may experience discomfort or respiratory embarassment due to increased intrathoracic pressure.

Bronchiectasis, Pulmonary Abscess and Neoplastic Disease

If there is no marked decrease in pulmonary reserve, the patient should be permitted to fly Marked dyspnea on exertion should rule out flying If the patient is expectorating foul sputum, consideration must be given to other passengers Such odors readily permeate the cabin, and are objectionable to others. In such patients, private air transportation is recommended if trips are urgent.

Pneumoconiosis

For patients with pneumoconiosis, if severe, flying is contraindicated, unless arrangements are made beforehand to provide 100 per cent oxygen for the duration of the flight

Foreign Bodies in the Lungs

Such cases may be transported at any time, because of the emergency, which may override all other considerations However, there are several dangers Complete obstruction of major branches of the bronchial tree and trapped gas present difficulties early Later, atelectasis may impair gas exchange, and the patient may become hypoxic Oxygen should be provided along with trained flight attendants

Pulmonary Fibrosis

Considerations are essentially the same as in emphysema.

Postoperative Conditions[16 18]

Tracheotomy patients should advise the airline, so that arrangements can be made to alter the oxygen mask to fit properly in the event that oxygen is needed

Lobectomy and pneumonectomy cases do not travel well under three months, postoperatively. They may fly in pressurized planes after fixation of the mediastinum Oxygen should be available for their use if necessary

At the 1958 meeting of the Aero Medical Association, Foley reported on 29 operations which included wedge resections, lobectomies and traumatic repairs on patients who later were returned to flying duties following operation. These cases included such diagnoses as lung abscess, diaphragmatic hernia, apical bullae and atelectasis A further report was given that wedge operations had been done on a few military pilots who had pulmonary tuberculosis with later a return to flying duties after one year's convalescence These patients are still under observation, however In the experience of this writer during the last five years, there have been two cases of bullae, which have been successfully operated upon, and the pilots have returned to flying A third chest condition was one of a lung abscess of the right middle lobe Following a lobectomy, and several month's convalescence, the pilot was returned to flying without any subsequent difficulty.

Medical Conditions Other Than Cardiopulmonary

Anemias

Patients with anemia may fly if their hemoglobin is above 60 per cent. Some physicians also recommend that the patients have a red blood cell count of over three million Oxygen should be available to care for any undisclosed hypoxia

Leukemia

Such cases may be flown provided their general condition is good It is preferable that they have a transfusion before flight and adequate oxygen available

Sicklemia[5 23]

Considerable evidence is available which indicates that when sicklemia patients are exposed to decreased oxygen tension, splenic infarction may develop Sickling disease variants (sickle cell-Hemoglobin C disease, etc.) in the presence of mild hypoxia corresponding to an altitude of 4,000 to 6,000 feet may develop splenic infarction. Little can be done to prevent this rare occurrence, except to recommend against flying for patients known to have this condition

Contagious Diseases

Patients with the usual contagious diseases are subject to the national, state or local public health laws or regulations These apply to air travel the same as in any other means of travel In international flights, these patients would come under the jurisdiction of the Foreign Quarantine Service of the United States Public Health Service They are not acceptable for travel at any time Severe penalties may be imposed on those concerned with intentional violation of these regulations Immunization against certain diseases is required for international travel. Consultation with airline medical services is recommended when trips to other nations are contemplated

Poliomyelitis

Patients with poliomyelitis may fly, if they are not confined in isolation, and provided the condition is not of the bulbar type If they are paralyzed to the extent that they cannot easily make use of toilet facilities, they should be accompanied by an attendant Air evaculation of patients who develop acute poliomyelitis in isolated areas has proven helpful, when proper equipment and travel attendants are available The U S Air Force Air Evacuation Service has had extensive experience in this field [32]

Diabetes Mellitus

This disease is not a contraindication to flying provided the patient does not require insulin during the actual time in the air or is able to administer his own insulin Such patients must carry on board their insulin and equipment for administration Diabetics with a tendency toward air sickness should take antimotion sickness pills before boarding the plane Sugar should be available to prevent hypoglycemia.

Pregnancy

Pregnant passengers may usually be flown without difficulty, within the first eight months of pregnancy, if there is no past history of premature birth or habitual abortion When necessary, pregnant women may be flown during the ninth month, provided their obstetrician will furnish a statement that in his opinion they are not expected to deliver within 72 hours of their proposed destination time It is also advisable for the individual to have a certificate stating that she is in generally good health, regardless of the month of pregnancy. It is always preferable for pregnant women to arrange their trips prior to the eighth or ninth month of pregnancy.

Infants

During the first 10 days of life, flight is contraindicated, since the respiratory system has not stabilized adequately at that age.

Mental Conditions[29]

Psychotics or agitated patients who may be dangerous or obnoxious to others, must not be permitted to fly In military air evacuation, psychotic patients are taken after proper sedation, but this practice is not recommended without experienced air crews and attendants. Neurologic patients should be ambulatory and have full bowel and bladder control These patients should be accompanied by trained attendants

Other Surgical Patients[12, 16, 18]

Those convalescing from abdominal surgery may be accepted for air travel provided at least 10 days have elapsed since the initial surgery, and the abdominal wall wound is not open or draining Uncomplicated peptic ulcer patients do well as a rule in flight However, if there is a possibility of perforation, flight should not be undertaken due to the relative pressure increase of the gas within the stomach or intestine at the higher altitudes. Passengers with colostomy bags should empty them just before flight, and may be acceptable for flight if they are nonodorous Passengers with large unsupported hernias should not fly due to the possibility that relatively increased intra-abdominal pressure may lead to strangulation, especially in the sitting position in the plane.

Strickland and Rafferty's report[16, 29] on 14,000 cases flown by the Military Air Transport Service recorded no symptoms in 93 per cent of those cases and no recorded deaths during flight There also was no interruption of flights due to symptoms

Air transporation proved so successful that in 1949 it was adopted as the sole method of

moving patients of the military forces The use of hospital ships and trains was discontinued The findings indicate that almost every patient suitable for transportation is transportable by air, provided that proper facilities are available either by ambulance plane or commercial aircraft.

Experience indicates that deaths occur on commercial aircraft at the rate of about one in every two million passengers There are no records available from other modes of transportation for comparison However, it is believed the number of deaths are so small as to indicate that flying is as safe for the average *patient-passenger* as is any other activity of daily life, so far as sudden death from natural causes is concerned.

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Spealman and associates: When the subjects are exposed for several days to uncomfortably warm temperatures in a "psychrometric" room, the concentrations of both plasma protein and hemoglobin decrease, whereas the total amount of plasma protein and total blood volume indicate substantial gains In the cold the concentrations of plasma protein and hemoglobin are increased with reduced total plasma protein and blood volume. These changes in hemoglobin concentration represent the dilution effect resulting from shifts in the plasma volume. This is confirmed by the fact that on exposure to either extreme environment, no appreciable change occurs in the total circulating hemoglobin as determined by the carbon monoxide method.[9]

Metabolic and Respiratory Adjustment

Under heat stress the total ventilation of resting normal subjects hardly rises above 20 liters per minute even at a rectal temperature of approximately 40 C, whereas the alterations in the respiratory rate and the tidal volume may vary depending on the heating method employed During the steady state, the O_2 consumption increases in proportion to the total ventilation, maintaining the ventilatory equivalent for O_2 (total ventilation/O_2 consumption) virtually constant before and during hyperthermia In effect, the metabolic response in hot environments obeys the general law of chemical reactions. The metabolic increment is best correlated with the mean body temperature which may be computed from the "core" and "shell" temperatures During the transient state of thermal hyperpnea, the alveolar CO_2 tension is reduced to 20 mm Hg or less with increased alveolar O_2 tension of 130 mm. Hg and an arterial blood pH of 7 80.

The evaluation of pulmonary ventilation at various body temperatures requires proper consideration of two important aspects. One is the differentiation between the steady and transient states of respiration as well as body temperature; the other, close examination of the altered physicochemical properties of blood due to temperature change During the transient state of either hyperventilation (in either hyperthermia or shivering) or hypoventilation

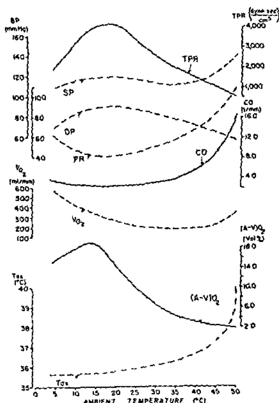


Fig 1 —Hemodynamic adjustment of man to thermal stress (Redrawn from Wezler[2]) Abbreviations T_{ax} = Axillary temperature, V_{O_2} = O_2 consumption; PR = pulse rate, BP = arterial blood pressure, SP = systolic pressure, DP = diastolic pressure, $(A\text{-}V)O_2$ = arteriovenous O_2 difference, CO = cardiac output TPR = total peripheral resistance

(during intensive hypothermia) the large reserve of bicarbonate is constantly adding to or subtracting from the alveolar gas Experimental studies (CO_2 inhalation) indicate that approximately 90 minutes are required to reach a reasonably steady level among the respiratory, metabolic and tissue stores gas exchange ratios at normal temperature[8] The second aspect concerning the effect of temperature on the chemistry of blood is much more complex and less well understood According to Austin and Cullen,[1] at least four major variables contribute to the temperature effect: (1) The solubility of both CO_2 and O_2 are increased curvilinearly with the reduction of blood temperature. (2) The value of pK′ increases with the reduction of plasma temperature (3) There is an upward shift of the CO_2 absorption curve as the temperature is reduced, a shift attributed to unequal changes in the dis-

Cardiopulmonary Response to Thermal Stress

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THERMAL homeostasis in health and disease is accomplished by quantitative equilibrium between production, dissipation and storage of body heat, which requires precarious regulation of pulmonary ventilation and circulation In hot environments, excessive heat influx is counterbalanced by the enhanced heat dissipation mechanisms of cutaneous vasodilatation and perspiration, leading to an increased skin temperature and peripheral blood flow In the cold, on the other hand, inordinate heat loss is promptly counteracted by the heat conservation mechanisms of cutaneous vasoconstriction and shivering

CARDIOVASCULAR ADJUSTMENT

The hemodynamic studies on man accomplished by Thauer and Wezler[10, 11] under the steady state in an all-weather chamber indicate a slow increase (less than 100 per cent) and then a steep rise (up to 400 per cent) in the cardiac output at the ambient temperatures of 40 and 50 C respectively (the corresponding axillary temperatures of 37 and 40 C), compared to the value at the environmental temperature of 25 C The maximal pulse rate of the resting subject in a hot environment rarely exceeds 120 per minute (reclining) or 140 per minute (sitting), in contrast to the tolerable rate of 180 per minute often seen during severe physical exercise Owing to the relatively greater increase of cardiac output in relation to the concomitant rise in the metabolic rate and the mean arterial blood pressure change, the arteriovenous O_2 difference (O_2 consumption/cardiac output) and the total peripheral resistance (mean arterial blood pressure/cardiac output) become progressively less as the environmental temperature rises The earlier observations by Grollman[5] and by Bazett and his associates[2] on cardiovascular essentially agree with most of the aforementioned findings.

In the cold, cutaneous vasoconstriction followed by the drastically reduced skin temperature and peripheral blood flow reverses the trends observed in hot environments: Within the ambient temperature range of 15 to 25 C , the cardiac output remains relatively constant The total peripheral resistance, however, increases probably in part due to the cutaneous vasoconstriction The increase in total peripheral resistance together with the unchanged cardiac output results in an increase in arterial blood pressure In addition, the arteriovenous O_2 difference becomes larger as the metabolic rate begins to rise with the onset of varying degrees of shivering activity In severe cold, the intensive muscular contraction of shivering induces a two or threefold increase in O_2 consumption as well as an accelerated cardiac output and a reduction in both total peripheral resistance and the arteriovenous O_2 difference It has been amply demonstrated that prolonged exposure of the extremities to very low temperatures (0 to 10 C) causes "cold-vasodilatation" and subsequently an increased peripheral blood flow [3] In such a case the heat loss from the periphery may increase well over five times the heat dissipation from the same region during cold vasoconstriction The circulatory response of man at different ambient temperatures (6 to 50 C) is schematically shown in FIGURE 1

Acclimatization to heat is associated with an increase in the blood volume. It appears that full dilatation of the cutaneous vessels cannot be attained without a redistribution of the body fluid, in particular, the blood volume Conversely, during acclimatization to cold, cutaneous vasoconstriction continues and the blood volume is reduced The mechanisms involved in this blood volume change in warm and cold environments have been studied by

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Introduction

UNDERWATER activities impinge on the field of physiology most emphatically in the area of diving. The terminology is confused, hence a few definitions are required A *skin diver* is a swimmer who submerges at various depths for extended periods of time During the dive his only air is that contained in his lungs, at surface pressure With descent, the volume of air is decreased as the air pressure in his lungs adjusts to the ambient pressure at the depth in which he is swimming He can remain submerged only as long as the breath is held Under the circumstances it makes no difference if the skin diver uses goggles, mask or snorkel-tube

The development of a pressure compensating demand valve by Cousteau and Gagnon during World War II has made it possible for aquatic sportsmen to utilize compressed air in portable bottles, thus extending the length of time the diver can remain submerged The self-contained underwater breathing apparatus (scuba), available in a variety of designs, supplies air through a mouthpiece or full face mask. The users of these self-contained units are called *sport divers* or *scuba divers*, preferably the latter term The traditional deep sea diver is dressed in a suit of heavy duck with a metal breastplate and helmet He receives his air through a hose from a supply on the surface

Because of the narcotic effect of high partial pressures of nitrogen it was found desirable to utilize a gas having a lesser narcotic effect Helium and hydrogen are two such gases. Hydrogen can form explosive mixtures when mixed with air or oxygen, an obvious disadvantage Helium is chemically inert in mixtures with oxygen and has much less narcotic effect than nitrogen In recent years, helium-oxygen mixtures have been used regularly for deep sea diving by the U.S Navy For economic reasons its use requires a modification of the helmet so the fullest possible utilization of the oxygen supply can be obtained The recirculation, thus achieved, necessitates arrangements for the removal of carbon dioxide.

While a diver may find himself in difficulty from the direct (mechanical) effects of pressure in terms of trauma to the air-containing cavities (sinuses, middle ear, bowel, lungs), the physiologic problems are primarily concerned with the indirect influences of pressure It is known that the narcotic effect of nitrogen relates generally to the depth of the dive, also the absorption of inert gas by the body (nitrogen in the case of air diving, helium in the case of helium-oxygen diving) during the descent and time spent on the bottom are the result of elevated partial pressure of the gas in the lungs With descent, the pressure on the breathing medium must be kept at slightly higher levels than the surrounding pressure of the water, otherwise, the external pressure on the chest wall will prevent inhalation As a result of the increased pressure at depth, the amount of inert gas present in the tissues increases during the periods of descent and while on the bottom

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If the ascent is slow enough, the gas will leave the body without causing any difficulty for the diver. However, if ascent is too rapid, the effect in the body would simulate uncapping of a bottle of carbonated beverage, with

sociation coefficients of H_2CO_3-$BHCO_3$ and H protein-B protein buffer systems. (4) Finally, the dissociation of water varies with changes in temperature. Recently, the importance of the dissociation of water at different temperatures has been re-emphasized by Winterstein [12]

It has been well established that the basal metabolic rate of residents in the polar area or of cold acclimatized animals is on the average from 15 to 30 per cent higher than that of those in the temperate zone The mechanisms of this increase, although debated for more than half a century, remain unknown Whether the increase results from greater muscular tone or from some "extramuscular" factor such as the calorigenic effect of adrenaline has not been established During vigorous shivering, O_2 consumption is doubled or occasionally tripled in direct proportion to the intensity of muscular contraction This is accomplished by a linear increase in the total ventilation with an unaltered respiratory exchange ratio (CO_2 production/O_2 consumption) The analysis of simultaneously obtained expired air and arterial blood reveals no significant differences in pH, P_{CO_2} and buffer base during the steady-state Nonetheless, the increase of alveolar ventilation as reflected in CO_2 clearance is considerably greater than that of the total ventilation, and this is achieved by a relatively greater increase in the tidal volume than the *respiratory rate As a whole, the metabolic demand* and ventilatory response during hyperpnea of shivering is strikingly similar to that seen during mild exercise [6]

Continuous exposure to severe cold eventually upsets the balance between heat production and heat loss, and the body temperature gradually falls At the "core" temperature range of 30 to 33 C the heat conservation mechanism of shivering begins to cease functioning Meanwhile, the cold narcosis also depresses the medullary respiratory centers inducing a gradual hypoventilation and CO_2 retention In theory, the effect of reduced body temperature *on the O_2 dissociation curve* is a shift to the left, but the respiratory acidosis produced by hypercapnea tends to oppose this transfer Moreover, the reduced blood flow may precipitate metabolic acidosis. It has been demonstrated in man as well as in experimental animals under hypothermia that the arterial blood is sufficiently oxygenated due to the retarded metabolic rate and the increased solubility of O_2 despite reduced respiration and blood flow [4] In addition, the concurrent determination of arterial and alveolar CO_2 tensions indicates no impairment of CO_2 transfer across the alveolar membrane when the body temperature is reduced [7]

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the formation and dissemination of bubbles. The manifestations include symptoms and signs that vary from fatigue, marble-like areas of the skin, itching, painful joints ("diver's bends") to frank formation of intravascular gas emboli with the serious implications of such a phenomenon

Theoretically, the diver should be able to descend at a fixed rate and then, if he started up at the moment he touched bottom, ascending at the same speed, the gas would leave his body as it entered. Such a manner of diving would have no practical value because of the limited time allowed at the bottom

Until 50 years ago, diving was a "catch as catch can" type of sport and occupation, learned by apprenticeship from a former diver who had been unable to continue with his occupation Recognizing the need for safe and exact methods, the Royal Navy called on the elder Haldane to develop a satisfactory method for removing the gas from a diver's body after a period of work on the bottom He developed the system known as stage decompression and through observation concluded that divers rarely experienced difficulty if they had not descended deeper than about 35 feet (33 feet of sea water is a pressure equivalent to two atmospheres absolute), no matter how long they may have been engaged at that depth From this he concluded that a diver could be brought directly to the surface even though the gases in his body tissues were in equilibrium with the same gases at two atmospheres pressure (a surfacing ratio of 2:1) By calculating the tension of gases in the diver's tissues on the basis of the duration and depth of the dive, he reasoned that a diver could be brought up to a depth at which the tension would be reduced by one-half Indeed, observations proved that while the diver was held at this depth the gas passed from his body, and as the exodus of the gas proceeded, the difference in pressure was reduced and the rate of exodus also reduced Then, the diver could be brought up further again, to reduce the pressure by one-half. This process could be repeated until the diver's tissues were equilized to two atmospheres absolute, permitting the diver to be brought to the surface with entire safety. From this concept, decompression schedules (tables) were developed which were characterized by a series of "stops" at 10 foot intervals Various periods were spent at each of the stops, usually longer periods at the shallower levels

Decompression for Air Dives

Single Dives (One Dive In 24 Hours)

In the field of decompression for air dives considerable re-examination of the situation has taken place since World War II in both the Royal Navy and the U S. Navy. The concept of decompression by stages, as developed by the elder Haldane and co-workers was published in 1908 and established the principles of making the fullest use of the differences in nitrogen pressure between the tissues and the ambient nitrogen pressure The idea was to hasten the elimination of nitrogen without exceeding a 2 1 ratio between the gas tension in the tissues and the ambient partial pressure of the gas In 1935, after a review of over 2,000 closely observed dives to depths varying between 100 to 200 feet, Hawkins, Shilling and Hansen suggested a modification in this fixed ratio A concept had been evolved of a series of hypothetical "tissues" having different periods of half saturation They calculated the maximum safe surfacing ratios to vary from 5 5 1 for the 5 minute tissue to 1 8:1 for the 75 minute tissue The chief practical effect of this work was to avoid unnecessarily deep decompression stops and offer the advantage of a greater head of pressure than Haldane's 2.1 ratio would provide

In 1937, Yarbrough described a procedure for calculating decompression tables These tables, employing more liberal ratios than those of Haldane, were the basis for decompression schedules used by the U S Navy for the next eighteen years Behnke approached the problem with measurement of nitrogen elimination and put the subject on more of a quantitative basis. He concluded that nitrogen was absorbed in proportion to the nitrogen partial pressure in the lungs, that nitrogen would pass in or out of the body at an equal rate for a given head of nitrogen partial pres-

sure. He also concluded that complete nitrogen equilibration with the atmosphere required the same period of time, and for corresponding periods nitrogen elimination took place at the same percentage rate, regardless of the total quantity of nitrogen absorbed. Van der Aue and associates, in their studies of surface decompression during long deep dives, found that surfacing ratios for all tissues should be less than the ratios previously considered safe for dives in the 100 to 200 foot range. The concepts of Bateman were essentially the same, except that he considered "people" rather than hypothetical "tissues" Essentially the same concept was offered by Piccard in terms of diminishing allowable supersaturation as the amount of dissolved gas in the tissues increased at greater pressures (longer, deeper dives) The development of computing machines made possible a more flexible, more exact and immeasurably less laborious means of calculating such tables. Prompted by the desires of underwater demolition units for decompression tables more suited to their needs, and especially decompression tables for repetitive dives (more than one dive a day), a re-examination of the available tables was undertaken The tables of Yarbrough were subjected to so many extemporaneous adjustments and rearrangements that they became unusable. Dwyer[4] compiled the data in a form suitable for programming a computer Dwyer's work elaborates the concept of Haldane in a form suitable for use as a didactic text The tables computed by the Univac were tested in the actual performance of working dives. Modifications were made on an empirical basis, were kept consistent throughout and were carefully documented The results were incorporated in a new Navy Standard Air Decompression Table, based on an ascent of 60 feet per minute to the first stop, with dives as deep as 190 feet for a 60 minute bottom time[2,6] The table is broken down into sufficiently small subdivisions of bottom time to provide adequate safe reductions in time spent in decompressing as compared with schedules noted in the previous table[9] It should be mentioned that dives not shown in the new table are considered as not requiring decompression (shorter, shallower, no decompression) or those beyond the range of usual practice in diving, such as longer, deeper and air saturation dives Physiologists will find interest in the observation that the surfacing ratios of the "tissues" have longer "half-times" than are usually considered critical[2]

Workman,[7] who utilized the tables during the testing program, has extended their application for long, deep, "air saturation" dives to cover situations encountered when a diver is trapped in the water He found it necessary to consider tissues having "half-times" of 120, 160 and 240 minutes using a surfacing ratio of 1 94.1[6,7] It appeared to Workman[7] that failure to recognize these aspects had posed limitations of earlier tables[9]

Repetitive Dives (More Than One Dive A Day)

Once the new tables for single dives had been proved by practical test and firm acceptable surfacing ratios for the various tissues had been established, it was possible to proceed with the establishment and testing of repetitive dive decompression tables[3,8] These employ the Haldane principle and provide a system by which a diver can determine the necessary increase in decompression time for the second and successive dives, based on the amount of excess inert gas tension in his body at the time of commencing his next dive By reference to the depth and bottom time of the first dive from either the No Decompression Table or the Standard Air Decompression Table (1956) the tender may determine the group (of 14) in which the diver belongs on the basis of excess inert gas tension still in his body when he surfaced From this group at the end of the surface interval and the depth of the proposed next dive, the time deficit is charged against the diver Accordingly, this time deficit becomes an expression of the excess gas in the diver's tissues remaining from his preceding dive at the time of commencing his next dive This time deficit is added to the time the diver expects to remain at the bottom following his second dive, and with this routine the decompression schedule is selected It will be noted that the tables are

limited to 190 feet and less because of the practical observation that a diver going any deeper while breathing *air does not recover* sufficiently, mentally or physically, *to make* another dive within 12 hours A 12 *hour surface* interval provides complete equilibration with ambient nitrogen pressures at the surface, and thus permits another dive The repetitive dive tables were tested in the facilities of the Experimental Diving Unit and later, by Lanphier, in sea trials on working diving jobs They have been soundly conceived and are safe to use in practice [6]

While the revision of decompression tables as described above was proceeding in the United States a similar re-evaluation was being followed in England by Hempleman, of the Royal Naval Physiological Laboratory [5] His project was to determine whether a ratio (Haldane's concept) or a pressure excess (*Rashbass' concept*) is the proper criterion to be used, and if so, should such criteria be regarded as pressure dependent He concluded that a ratio is the criterion to be used and that it is constant with pressure, but it applies only to single drops in pressure (first stop) He expressed a suspicion which had become evident among several workers in the field that saturation and desaturation are not reversible phenomena, at least for nitrogen. He also pointed out that many of the physiologic phenomena in diving can be explained only by involving the "silent bubble," a bit of diving folklore. Practically all explanations of the phenomena of diving casualties rely on the assumption that gas passes out from the state of supersaturation in the tissues to form a bubble, the nature and severity of the symptoms and signs being related to the size and location of the bubble As for example, the extreme fatigue often observed after exposure to pressure and other vague manifestations are attributed to "silent bubbles"

Following the unsatisfactory use of the tables at sea, as based on the single tissue concept of Hempleman[5] and the pressure difference concept of Rashbass,[29] Crocker[1] has added a "bubble regression" curve to the approach He considers this curve to represent the relationship between tissue saturation, *bubble size* and bubble pressure which regulates the speed of safe ascent Tables so constructed *have been tested in the chamber and* at sea With slight modification they have offered considerable operational advantage with *reasonable safety*

Adaptation of Skin Divers

Skin diving with goggles or facemask, with or without a snorkle has provided many happy hours for seashore vacationers Schaefer[13] has had the unique opportunity to study a group of skin divers who practiced the sport as a day by day occupation, notably, the instructors at the Escape Training Tank, U S. Naval Submarine Base, New London, Connecticut. In the performance of their duties, the divers made their dives while holding their breath, to depths as great as 100 feet From time to time, they also were exposed to compressed air for periods of about 20 minutes at various depths down to 100 feet Schaefer found that the divers in the course of a year learn to *breathe differently while developing a tolerance* to elevated alveolar CO_2 levels not shown by others Their vital capacity increased an average of 14 6 per cent above the predicted figure as based on the formula by West This was accompanied by increases in the inspiratory reserve and the tidal volume Further studies of some 60 subjects with various occupations indicated that such men could be divided into two groups on the basis of their ventilatory response to carbon dioxide Those with a low response showed a 2 mm higher alveolar CO_2 tension, a lower respiratory rate and a larger tidal volume than those in the high response group When breathing various concentrations of CO_2 up to 7 5 per cent, *the* low response group showed less change in the pulse rate, blood sugar and eosinophile counts The differences between the groups were correlated with the variations in adrenal sympathetic response, the more effective skin divers followed the pattern of the *low response group. After a three month* vacation from underwater work, members of the skin diving group displayed low response characteristics This suggested an adaptive mechanism to the stresses of skin diving

Scuba Diving

The widespread use of scuba diving has created a general interest in the body economy of underwater swimming and in the physiologic hazards of diving as related to sportsmen The sport has become so popular and widespread that no medical practitioner is so isolated or so specialized that he may not find a self-appointed frogman brought to his doorstep from some neighborhood puddle Great depth is not necessary for the tragedies of diving Thus, every physician should be informed of the fundamentals of diving medicine The life he saves may even be his own The medical problems and hazards have been documented adequately[9, 11, 12 14], and the technic of scuba diving is set forth.[8-10] It has remained for Lanphier[21] to transport the clinical aspects of body economy of underwater swimming for laboratory investigation He developed further the underwater trapeze, a device employed by the Cooperative Underwater Swimmer Project (NRC.CAO 0033) in 1953. Utilizing the unusual facilities of the U S Naval Experimental Diving Unit he was able to equate underwater swimming with other physiologic studies of work [27]

Figure 1 is a series of curves showing oxygen consumption rates versus speed for several modes of travel Figure 2 shows the oxygen cost per unit of distance traveled versus speed for the same activity It is apparent from

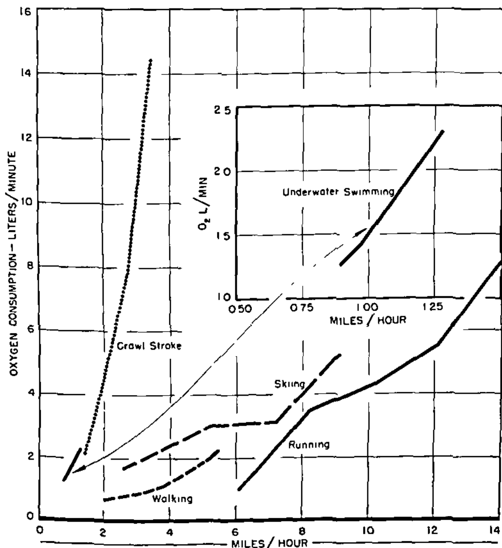


Fig 1—Oxygen consumption rates versus speed (approximations)

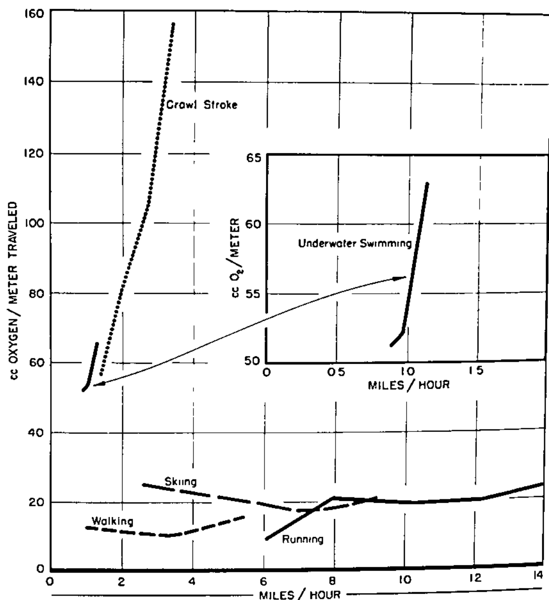


FIG 2—Centimeters of oxygen consumed per meter traveled versus miles per hour (approximations).

these representations that swimming is not an economical means for travel nor is it mild exercise as compared with other forms of physical pursuits This should provide critical evidence for advising the would-be swimmer or deep water diver; namely, that he should be physically fit to swim before taking up the sport of diving

The importance of the above evaluation is emphasized in the light of other forms of work, such as lifting weights and riding a bicycle, which often give rise to misleading concepts The speed of underwater swimmers falls under a relatively narrow range, particularly if it is sustained for any considerable length of time Lanphier's subjects regarded 0 5 miles per hour as too slow, because it caused difficulties with maintaining depth On the other hand, 1 14 miles per hour rapidly produced either respiratory or muscular fatigue and limited the duration to less than 20 minutes for most underwater swimmers There has been general agreement that a speed in the range 0 9 to 1 0 miles per hour would serve best for a long swim From this evidence it is apparent that swimming against a current or tide is a losing proposition. The reference to the limitation of breathing fatigue emphasized the importance

of a low-resistance type of equipment and should discourage the do-it-yourself participants from making their own equipment

Oxygen Consumption

Considerations of speed versus efficiency (oxygen consumption versus distance traveled) have suggested that each swimmer has an individual speed capacity beyond which efficiency decreases and that this favorable speed is close to the most "comfortable speed" There may be a considerable difference in oxygen consumption between the "experienced" and "novice" swimmers, an indication of the sound physiologic basis for advising that "buddies" should alternate taking the lead and setting the pace when swimming together.

Oxygen consumption rises as speed of swimming increases, but beyond 0 9 miles per hour this increase may be more pronounced There are wide variations in the rate of oxygen consumption between individuals swimming at the same rate not accountable by variations in size There are similar wide variations from day to day with the same individual. The oxygen consumption values obtained by Lanphier and Dwyer for experienced swimmers is shown in TABLE 1 The mean oxygen consumption for the four inexperienced underwater swimmers at 0 91 miles per hour was 1 59 L per minute in contrast to a value of 1 30 L per minute for the experienced group

Shallow Water Blackout

In the course of Lanphier's studies of oxygen consumption by underwater swimmers[23] there were three cases of shallow water blackout, clearly related to elevated carbon dioxide levels These episodes were linked with exhaustion of the absorbent Lanphier verified this by donning personally the equipment of a scuba diver and swimming until symptoms appeared These experiences have warned sportsmen "never to use oxygen (closed circuit) scuba"

An interesting observation, modifying the above concept of carbon dioxide poisoning is the occurrence of "underwater syncope" described by Miles[16] His review of 43 underwater incidents revealed the following explanations:

TABLE 1 —*Oxygen Consumption of Experienced Underwater Swimmers** (Mean Values and Range, 6 subjects, Liters of oxygen, STPD, per minute)

Underwater Speed *Miles per Hour*	Mean	Low	High
0 57	0 82	0 67	1 00
0 68	0 96	0 83	1 14
0 80	1 14	0 96	1 35
0 91	1 30	1 04	1 52
1 02	1 53	1 13	1 90
1 14	1 83	1 34	2 26
1 25	2 10	1 56	2 64
1 36	2 50	1 87	3 03
Rest	0 34	0 26	0 41

* From DWYER, J V, AND E H LANPHIER, E D U Research Report 14-54, Dec 22, 1954

UNCONSCIOUSNESS

Syncope

- free swimmers, anoxia following hyperventilation, 3 cases (syncope)
- oxygen scuba, combination of breathing 100% oxygen, inexperience, anxiety, hyperventilation, fatigue, sudden raising of intrapulmonary pressure, hunger, alcoholic hang-over, heavy meal, and poor vaso-motor tone, 19 cases (syncope)
- inexperience, anxiety, 6 cases (near syncope)
- epilepsy, 2 cases
- oxygen poisoning, 2 cases
- *fatigue, acute infection*, 1 case
- inexperience, panic, near drowning, 1 case
- faulty use or faulty equipment, 8 cases

Fatalities; 6 cases

- Anoxia—2, O_2 convulsion—2 shark bite—1, unknown—1)

The important point for the sport diver is that all the cases of true syncope (19 cases) occurred in men using oxygen scuba Failure to purge properly the counter-lung with oxygen, exhaustion of the oxygen supply or failure of the carbon dioxide absorbent, singly or in combination, played an important role in three cases of underwater unconsciousness and two of the fatal cases These observations do not disregard the potential danger of carbon dioxide poisoning but rather emphasize the wide variety of contributing factors in syncope.

Oxygen Toxicity

Oxygen toxicity is a threat to those who use closed circuit (oxygen charged) scuba. Schaefer[30] studied a group of experienced underwater swimmers while performing at an average speed of 0 98 miles per hour. Their depths were 20, 30 and 40 feet while breathing oxygen in a pattern of alternating swimming and resting He reported a general downward trend in pulse rate values at the beginning of each succeeding rest period while the respiratory rate increased. He noted also that when the pulse rate failed to respond to exercise or rest symptoms of oxygen toxicity followed in 78 per cent of the cases This "fixation of the pulse rate" was interpreted as parasympathetic activity. This was considered as a warning sign of impending oxygen toxicity When the test swim was stopped because of symptoms, the pulse and respiratory rates were found significantly elevated This suggested to Schaefer that an increased sympatheticotonic activity accompanied symptoms of oxygen toxicity The dyspnea observed under these test conditions was usually characterized by rapid, shallow breathing with apparent inspiratory inhibition. The onset of symptoms was definitely related to elevated partial pressures of oxygen and not to the partial pressure of CO_2 The possible relationship to dominant vagal tone was considered Schaefer postulated three phases of physiologic activity first, development of a strong parasympathetic activity with decreased pulse rate, second, dominance of parasympathetic activity, failure of pulse rate responsiveness to exercise and rest, preceding the onset of symptoms, third, symptoms of oxygen toxicity with increased sympatheticotonic activity. Although Lambertsen demonstrated that closed circuit scuba diving could be used safely by well disciplined and motivated participants, such activities could scarcely be followed without danger by the week-end sportsmen divers For this reason a warning against closed circuit (oxygen charged) scuba is valid and should be strictly observed

Mixed Gas Scuba Diving

The possibility of using helium-oxygen mixtures in deep sea diving was first proposed in 1919 by Elihu Thomson who predicted that the maximum depth of dives might be increased by 50 per cent. In 1925, Sayers, Yant and Hildebrand recommended such mixtures as a means of mitigating caisson disease They estimated that decompression time might be reduced to one-sixth of the expectant period Sayers and Yant, on the basis of animal studies, modified this view but suggested that decompression was more rapid with helium than nitrogen. In 1937, End briefly considered the possibility of diving with combinations of oxygen, helium and nitrogen Helium-oxygen was tested practically and proved successful in 1939 in the salvage of the USS SQUALUS Since Sweden had no source of helium, Arne Zetterstrom in 1945 developed a method of diving with a mixture of oxygen, nitrogen and hydrogen He proved the value of such mixtures but in the demonstration he lost his life In 1953, Lanphier and his associates while stationed at the Experimental Diving Unit, studied the use of mixtures of nitrogen and oxygen, other than air, in scuba equipment

Nitrogen-oxygen mixtures Two objectives may be attained with satisfactory decompression tables for a mixture of nitrogen and oxygen approaching equal parts of each gas It is considered that the hazard of oxygen toxicity associated with closed circuit scuba and the dangers of nitrogen narcosis and decompression sickness associated with open circuit scuba may be reduced by a mixed gas scuba On the basis of the curve of air dives requiring no decompression in the standard Navy Decompression Tables,[9] a series of curves for various mixtures of nitrogen and oxygen was calculated. For this purpose, a "toxicity curve" for time and depth of exposure to oxygen was constructed from available data and tested for nonappearance of symptoms The curves were superimposed to indicate an area of time and depth presumably safe from the hazard of oxygen toxicity or the problems presented by nitrogen Test dives in this area have given such erratic and unexpected results that a further search was instituted.[24] There was evidence which indicated that certain individuals during exercise and while breathing increased partial pressures of oxygen or air under pressure showed a relative decrease in pulmonary

ventilation and respiratory response to carbon dioxide. The unexpected results posed the question of summation of the effects of oxygen, nitrogen and a depth effect. Lanphier in an effort to compose this confused situation presented evidence that breathing a 55 per cent nitrogen-45 per cent oxygen mixture while swimming underwater caused a significant rise in end tidal carbon dioxide levels.[25] This was due apparently to a decrease in effective pulmonary ventilation. The levels of carbon dioxide as observed were capable of causing symptoms of carbon dioxide intoxication, and indeed such symptoms were observed. This work suggested rather definitely that nitrogen in some way was responsible for a damming up of metabolic carbon dioxide, emphasizing to the scuba diver that controlled breathing is a dangerous method of extending the duration of the air supply. It is possible that the breathing pattern of divers may in part be responsible for the CO_2 retention observed. Miles[28] studied the effects of increased pressure on the maximum voluntary ventilation (closely akin to maximum breathing capacity) and noted reductions related to depth in the following manner: 33 feet, 27.3 per cent, 66 feet, 41.1 per cent; 99 feet, 48.9 per cent, 150 feet, 50.5 per cent; 200 feet, 51.7 per cent. Similar reductions in MVV were found in experiments with a mixture of 8 per cent oxygen 92 per cent helium located 66 feet deeper. The matter of mixed gas scuba diving continues in an unsatisfactory state.

Are there human amphibians? An outgrowth of the studies of Schaefer[49] and of Lanphier[24] is the interesting suggestion that it may be possible to categorize humans roughly into those who are strictly land animals and those who have some of the characteristics of an amphibian on the basis of their response to carbon dioxide. The subjects studied by Lanphier could be separated into two such groups according to their response to underwater swimming. This was followed in a joint undertaking using the facilities of Lambertsen at the University of Pennsylvania in which only the "amphibian" types were studied. The results in the laboratory confirmed the "underwater" findings. During effort there was an increase of the internal carbon dioxide tension in the "amphibian" types to levels higher than in "dry land" subjects. This suggested that factors other than physical development or fitness accounted for the response of the "dry land" subjects.

The response to physical effort is usually characterized by the formation of fixed acid (chiefly lactic acid) which produces a degree of metabolic acidosis with an appreciable decrease in blood bicarbonate concentration and pH. This favors either a slight increase or no change in respiratory exchange, with a tendency for pH to return to normal and for a slight further decrease in bicarbonate to occur. The "amphibians" in general show an increase of fixed acid with a decrease in bicarbonate ion concentration. However, the P_{CO_2} actually increases instead of showing the expected compensatory decrease. Thus, both the metabolic and respiratory trends are in the direction of acidosis. As a consequence, bicarbonate levels remain higher than would be expected if a respiratory reaction had occurred.[25] Other similar studies have been undertaken, using helium-oxygen mixtures.[24]

The consolidated data from Lanphier's studies are shown in TABLE 2. Examination of these data shows that almost all of the factors involved in underwater swimming can influence carbon dioxide regulation. Most important is that breathing 45 per cent oxygen with nitrogen gives higher P_{CO_2} values than breathing the same concentration of oxygen with helium. Only added dead space in air breathing gives comparably high values. These results emphasize the importance of equipment design in reducing dead air space and in holding breathing resistance to the minimum. If mixed gas diving is to be developed, helium-oxygen mixtures should be considered in future development. Finally, as Lanphier concludes, there is a wide variation in respiratory response to carbon dioxide, however, there is no method of separating the "dry land" humans from the "amphibians" in a manner useful for selection purposes.

Schaefer's studies covering several years, conducted in the Laboratories of the Medical Research Laboratory, and in the Escape Training Tank, U.S. Naval Submarine Base, New London have included a wide range of

TABLE 2 —*Respiratory Response of Underwater Swimmers Various Breathing Media, Various Conditions, Various Depths*

Activity	Depth	Breathing Medium	End Expiratory P_{CO_2} (mm Hg)	Resp Minute Volume (l /min)	Resp Rate (breaths/min)
Work—swimming on trapeze equivalent to 0 96 miles/Hr	Surface	Air	47 1	28 2	11 0
		Oxygen	48 3	25 6	10 1
	99 Feet	45% oxygen with nitrogen	51 3	22 6	9 6
		Helium	44 6	25 0	10 1
		Air	49 4	20 9	10 1
		5-7% oxygen with nitrogen	48 6	23 3	11 3
		Air with minimal dead space	47 8	19 1	9 9
		500 cc added dead space	53 7	26 5	12 1
		Air	49 0	21 8	10 5
		45% oxygen with nitrogen	50 6	20 9	10 4
		Air	49 8	20 7	10 9
		45% oxygen with helium and resistance	57 5	19 0	9 4
Rest	Surface	Air	38 4	8 7	5 8
		Oxygen	38 9	9 6	6 5
	99 Feet	Air with minimal space	37 6	7 7	5 3
		500 cc added dead space	41 6	12 3	7 9

Each pair of conditions represents a set of runs in which a shift was made from one condition to the other during each run Resting values were obtained during the same runs as the corresponding values for work (From LANPHIER, E H E D U Report 7-58, June 30, 1958)

subjects and methods [19] He has concluded that the relationship between respiratory rate and tidal volume constitutes a pattern which permits the classification of "low response" and "high response" groups relating to their response either to high CO_2 or low oxygen Some subjects were not clearly in either group but rather in a zone of transition between the two groups; there were also subjects with a respiratory pattern so irregular that they could not be classified When experimental conditions were adequately controlled, the basic respiratory pattern and the response of CO_2 were fairly constant There has been the suggestion that the difference in the respiratory response to CO_2 is related to a difference in the adrenal sympathetic response to CO_2

Helium-oxygen mixtures. Duffner has reexamined the evidence relating to helium-oxygen mixtures. Certain data suggest that for many dive schedules the hazard of decompression is considerably less with 80 per cent helium-20 per cent oxygen than with air.[21] This represents a return to the concepts of Thomson regarding depth and those of Sayers and Yant as to the duration of decompression The fact that helium-oxygen mixtures were not used is apparently because of difficulties in the early attempts to compose appropriate decompression schedules Helium-oxygen mixtures have taken an added importance since they made possible a dive to very great depths (600 feet) by a diver of the Royal Navy in 1956

Duffner found that most of the helium can be taken up from an 80 per cent mixture in "tissues" having half saturation times between 1.5 and 5 minutes;[21] a small quantity is taken up by tissues with half-times between 95 and 115 minutes Since such a relatively

small amount of helium is taken up by tissues with half saturation times near the practical duration for scuba dives, it appears that this portion of the helium offers no major hindrance to the use of heluim-oxygen mixtures in mixed gas scuba diving. Since this latter helium fraction is so small, it can be ignored for practical purposes, thus permitting the use of the "single tissue" theory in this situation The single tissue concepts of Hempleman and Rashbass represent the first serious departure from the concepts of Haldane. Rashbass had developed a convenient concept in the "foots-worth," or that quantity of gas man's body will take up during an infinitely long exposure at a depth of one foot. Air decompression tables calculated on this basis have not been checked critically in sea trials

Dives with a 20 per cent oxygen in helium mixture to depths of 200 feet for as long as 180 minutes have been performed by Duffner's group with no greater risk of decompression sickness than would occur from air It was concluded, therefore, that a man can surface safely at a rate of 60 feet a minute following relatively long exposure to 80 per cent helium-20 per cent oxygen at 37 feet (37 foots-worth) Further, a rate of ascent of 75 feet per minute gives only minor symptoms following a dive to 120 feet for 35 minutes, and a rate of 120 feet per minute may be used between 120 feet and 30 feet The important practical applications as compared with current practice are that faster rates of ascent can be used near the surface and that a greater excess pressure of helium (20 per cent oxygen with helium) can be tolerated than of nitrogen (air). It has been found that a safe curve of "no decompression" dives can be formulated, using the square root equation

$$Q = 2D\left(\frac{\lambda t^{1/2}}{\pi}\right)$$

A value of 0 003 may be used for λ, Q is the quantity of gas taken up in foots-worth; D is the depth expressed in gauge feet However, use of this formula in computation of schedules for dives requiring decompression has predicted stop times about 67 per cent longer than required by experiment

Air Embolism

For years, physicians trained in diving medicine have proceeded with the hypothesis that at some critical overpressure inside the respiratory tract a break in the pulmonary membrane occurs through which air can escape into the tissues, causing emphysema, or into the vascular bed with resulting air embolism X-ray evidence of mediastinal emphysema following a casualty in submarine escape training (a form of diving activity) had been presented by Schulte[20] Kinsey[13] has reported the occurrence of neurological symptoms following similar casualties Fatal and nonfatal casualties during submarine escape training, even with trainees who apparently had made a proper escape, long ago gave rise to a suspicion the untoward effects could be explained only by segmental blocking of egress air. Liebow and associates[15] recently reported two cases (one fatal) of localized lung distension The fatal case at autopsy revealed a broncholith acting as a ball valve with complicating distension and trauma distal to the site Schaefer, McNulty, Carey and Liebow[18] in studies of air embolism in animals found that neither air embolism nor emphysema will occur unless two conditions prevail, the lungs must be completely distended and a critical intrapulmonic pressure 80 mm Hg must be exceeded They observed, however, that air embolism could be presented by binding the abdomen and thorax The critical factor, in their opinion, was not so much the absolute level of the intratracheal pressure, but rather a transpulmonic presure in excess of 60 to 70 mm. Hg, or a transatrial presure in excess of 55 to 65 mm Hg.

Submarine Operations

Schaefer[19] has studied the effects of long-extended exposures to low levels of carbon dioxide and has compiled important data on the subject. Various systems of the body have been studied in animals and, to the extent possible, in man. This work, although too

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voluminous to report in the present chapter, indicates that almost every response to elevated levels of carbon dioxide can be demonstrated in some degree during exposure to lower levels providing the exposure is maintained for a sufficiently long period of time. It appears the body is able to make some adjustments to carbon dioxide and can function at this new level Reversal of this adjustment requires a period of time equal to the period required to establish it in the beginning

The most striking physiologic data on the operations of nuclear powered submarines are not especially concerned with radiologic health practices or exposures Instead they are old problems in a new guise Never before in the history of the human race has man existed for such long periods of time in a sealed chamber In the fall of 1958, USS SEAWOLF remained continuously submerged for 60 days The oxygen in the air present at the time of submergence was used up long before surfacing Equally important was the problem of removing the carbon dioxide produced by the crew It should be mentioned that the nitrogen contained in the ship was breathed over and over again by the crew, and of the same percentage in the ship at the end of the voyage In this sealed chamber situation, the repeated addition of even trace quantities of air contaminants was of some importance Indeed, the possible exposure of men to very low levels of contaminants for very long periods of time presented an entirely new facet of toxicology, existing nowhere else, never before known In this situation commonplace occurrences become major problems For instance, cigarettes were regarded as carbon monoxide generators, and common floor wax, lighter fluid and shellac as dangerous articles. Indeed, a new field of toxicology had appeared with the perplexing problems of choosing tests for toxicity Here, there was no interest in lethality, a demonstrable lesion, or even in the derangements of chemistry The tests of toxicity here require repeated measurements of performance, mental function, emotional stability and similar functions We may look forward to the progressive development of new knowledge in this interesting area of investigation.

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the relationship between wind speeds in miles per hour (mph) and dynamic pressures are shown in the last two columns of TABLE 1. For orientation it is well to point out that hurricane winds of 120 mph exert a dynamic pressure of only 0 25 psi which fact emphasizes the very high winds that are associated with blast-produced overpressures.

Blast damage to structures and to biologic media are directly or indirectly caused mostly by either pressure variations, winds or both It is appropriate now to look to the scope of the blast problem from the biologic viewpoint.

SCOPE OF BLAST BIOLOGY

It is convenient to set forth the variety of problems related to the biologic effects of blast under four arbitrarily chosen headings which will now be noted and discussed

PRIMARY BLAST EFFECTS

Damage to a biologic target due to blast-produced variations in environmental pressure is spoken of as primary blast effects As a general rule, pathology is most marked in the air-containing organs—the lungs, gastrointestinal tract, the ear and paranasal sinuses—and at those locations where there is the greatest variation in tissue density Too, there may be effects at a distance which are a consequence of damage to the air-containing organs For example, there may be malfunction of the central nervous system or failure of the heart from vascular occlusion due to air emboli that actually enter the circulation in the lung and reach the peripheral vascular bed via the left heart

SECONDARY BLAST EFFECTS

Secondary blast effects are those due to missiles energized by blast overpressure and winds and sometimes by gravity should a structure be partly destroyed by blast and subsequently fall of its own weight Medically, such problems can be somewhat similar to the usual ballistic ones encountered in war medicine

TERTIARY BLAST EFFECTS

Blast damage of a tertiary character may occur as a consequence of the physical displacement of a biologic target by blast winds Biologically, injury may happen during the accelerative or decelerative phases of displacement Except for violent acceleration of different portions of the body, such as from small charges of high explosive when digits or extremities may be macerated and destroyed, violent decelerative impact comprises the major hazard Impact against a hard surface at 21 feet per second (15 mph) is sufficient to fracture over 90 per cent of human skulls.[25]

TABLE 1—*Approximate Relationship Between Incident, Reflected, and Dynamic Pressures and Wind Velocities Calculated for Sea Level Conditions*

Max Overpressure in psi			Wind Velocity in mph
Incident	Reflected	Dynamic	
1	2	0 02	40
2	4	0 1	70
5	11	0 6	160
10	25	2	290
20	60	8	470
30	90	16	670
50	200	40	940
100	500	125	1500

Psi = pounds per square inch

PRIMARY BLAST EFFECTS

PHYSICAL-BIOPHYSICAL FACTORS

The discussion that follows will deal only with several selected aspects of primary blast effects Related physical factors will be noted first followed by remarks more biologically oriented.

Spalling effects When a shock or pressure front travelling through one medium attempts to pass an interface with another medium of less density, there occurs at the interface a negative reflection which produces local tension in the first media As a result, the surface of the heavier media fragments or "spalls" Similar events can involve "spalling" and dust formation inside closed structures exposed to blast[17, 51] and are also noted when an underwater blast wave reaches the surface where negative reflection occurs and water particles are thrown into the less dense air, causing the "spray dome," a whitish mound of broken water well known in underwater demolition work [14]

— 63 —

Blast Biology

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INTRODUCTION

THOUGH the pathophysiology associated with the exposure of man and animals to blast from bombs and other explosive sources has been studied and fairly well documented over the years,[3, 16, 28, 44, 46, 52, 56] a renewed and broadened interest in the subject has developed since the first atomic explosions in 1945[5, 6, 9, 10, 40a, 50] At present, no thorough understanding of all facets of the subject exists, but it is nonetheless true that many of the physical and biophysical factors associated with *blast hazards from modern, high-yield detonations* are better appreciated than in the past. Too, additional data of a quantitative nature relating biologic damage to measured alterations in the environment have become available during the last decade[49a]

BLAST PHYSICS AND TERMINOLOGY

Whether energy is suddenly released through chemical processes as occur on detonating conventional high explosives, or created from a change in mass as happens in nuclear explosions, there emanates from the source—exploded in air—a pressure pulse that travels radially through the atmosphere. The magnitude of the pressure, usually expressed in pounds per square inch (psi), measured side-on *to the advancing wave is spoken of as the incident* or *local static pressure.* The duration of the pressure above the ambient—the *overpressure*—is measured in time units that may be a few fractions or tens of milliseconds (msec) for high explosives and few tenths to tens of seconds for large nuclear explosions The overpressures and their durations vary with explosive yield and distance from the detonation, e g , for a given weight explosion, *the overpressure decreases with distance,* while its duration increases with increasing range

At any given point, depending on the geometry, range, terrain and nature of the explosion, the rising phase of the pressure pulse may either be fairly slow, as might occur inside a heavy building, with gas entering through doors and windows, or almost instantaneous as frequently occurs in the open. In the latter case a shock wave often comprises the leading edge of the pressure pulse, and when such is the case, a high, pressure reflection can occur when the front impinges against a solid object or a *biologic target The magnitude of the reflection* may be two- to nine-fold the incident pressure, depending among other things on the magnitude of the latter The first two columns of TABLE I show the approximate relationship between selected incident and reflected overpressures calculated for sea level conditions

After a blast-produced overpressure passes a given point there follows an underpressure which is much *less* in magnitude and *longer in* duration than the overpressure The overpressure and underpressure pulses are accompanied by winds which blow away from and toward the explosive source, respectively. The force exerted by blast winds is called the *dynamic pressure* and is measured as the difference between the head-on and side-on pressures The positive winds are much the *greater in magnitude and some appreciation of*

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By permission of the Atomic Energy Commission this chapter was summarized from document TID-5764[50a] and the reader is referred to this reference for the full text, along with quantitative animal data and their relation to nuclear explosives

biologic target and penetrating inward is the transfer of momentum to different portions of the organism At the surface, for example, equal momentum might be imparted to two equal volumes of tissue in an amount related to the magnitude of the reflected pressure, but the resulting rate of movement of each volume would depend on their respective masses, e g, the velocity of the lighter mass would develop more rapidly and rise to a higher value than would be the case for the heavier one As a result of this inertia difference, local stresses and shearing forces would develop. Such considerations, for example, offer a reasonable explanation for the hemorrhagic areas often localized linearly along and near the junction of the intercostal tissues and the ribs as commonly seen and described by those familiar with blast-produced pathology.

Pressure differentials Before turning to the biologic response to "short" and "long" duration overpressures rising to a maximum in different times, it is instructive to employ simple models to aid in visualizing certain qualitative relationships between environmental pressures external to an animal and those that might be expected internally in the gaseous and fluid phases of the lung at the alveolar level

Consider FIGURE 1 which diagrammatically represents the trunk of an animal with the thorax above and the abdomen below The trachea is shown, with a constriction representing the bronchiolar resistance to air flow, leading to a "box" representing the gaseous phase of the lung. Protruding into the gaseous phase, another "box" is shown representing the fluid phase of the thorax, including the vascular components The latter communicates with the vascular elements below the diaphragm also shown as a "box" in the abdominal region

The lower portion of FIGURE 1 represents a situation in which the environmental (external) pressure is assumed to rise slowly and to a modest degree Under such circumstances, there is time for air to flow through the airways into the alveoli of the lungs at a rate which keeps the internal gaseous pressures increasing apace with those in the environment and liquid phases of the abdomen and thorax If the pressures are

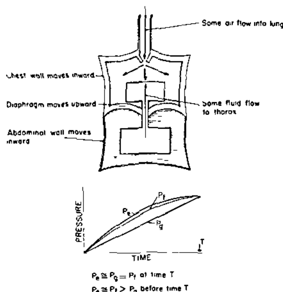


FIG 2—Diagram of model response to "slowly" rising overpressures to which "protective" response is effective

not too high and prolonged, there would be no hazard

FIGURE 2 shows a faster rate of pressure rise which does not allow time for gas to flow through the small airways into the alveoli in sufficient quantity and the rise in internal gaseous pressure lags below the external and liquid pressures There results some movement of liquid into the chest, a compression of the abdomen and thorax, elevation of the diaphragm and a *decrease in thoracic gas volume* As a consequence of the latter, particularly, the gaseous pressure in the thorax will rise and reach the level of the external pressure at some time, *T*, without development of serious events, providing the rise of the external pressure is not too high

In FIGURE 3, a more rapid and higher pressure rise was assumed which, even after sharp maximal inward movement of the perimeters of the thorax, results in external and liquid pressures well above those in the gaseous portions of the lungs Under such circumstances, blood moves toward the regions of lower pressure (squeeze syndrome), and rupture of the pulmonary vessels and lung hemorrhage results.

FIGURE 4 diagrammatically represents the results of a sudden, almost instantaneous rise in environmental pressure of relatively short du-

Schardin[46] has pointed out that such phenomena could occur at the fluid-air interfaces of the delicate pulmonary alveoli and result in fragmentation, edema and hemorrhage, providing a pressure pulse of sufficient magnitude emanated inwards from the body surface, and energized by a sharp application of force or pressure

Implosion effects Likewise, of potential importance in the etiology of blast damage to the lungs is the implosion effect, a term that Schardin[46] uses to cover phenomena which are seen when an explosive-produced shock wave travelling in relative incompressible water passes over small air bubbles The latter, being compressible, undergo a sharp decrease in volume with the development of very high, local pressures In fact, each bubble so "imploded" becomes the source of a "new" detonation and multiple shock waves emanate radially from the pulsating pressure in the gaseous phase. It is quite possible that damage to the air-containing portions of the lung can occur from implosion when an organism is exposed to blast overpressures Clemedson[11] has shown by direct means that shock fronts exist in and propagate through body tissues after the surface of an animal is struck by an explosive-produced pressure pulse travelling in air to reach the biologic target The consequences of such phenomena taking place near the alveolar regions of the lung are not known with certainty, but it is likely that considerable pathology does occur both to the thin alveolar walls and the more fragile vessels of the pulmonary vascular bed

Inertia considerations Yet another effect of a shock front reflecting from the surface of a

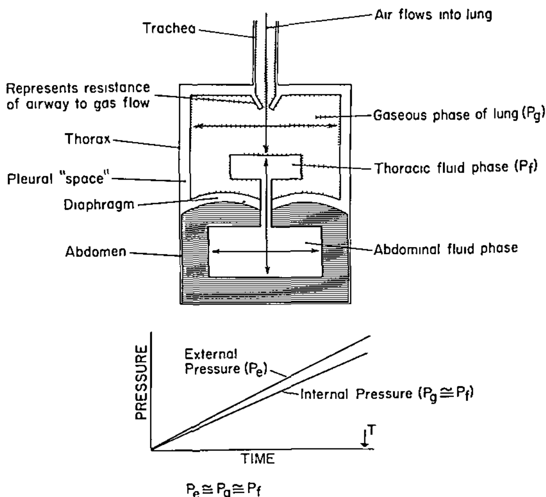


FIG 1—Diagram of model response to very "slowly" rising overpressures

biologic target and penetrating inward is the transfer of momentum to different portions of the organism. At the surface, for example, equal momentum might be imparted to two equal volumes of tissue in an amount related to the magnitude of the reflected pressure, but the resulting rate of movement of each volume would depend on their respective masses; e.g., the velocity of the lighter mass would develop more rapidly and rise to a higher value than would be the case for the heavier one. As a result of this inertia difference, local stresses and shearing forces would develop. Such considerations, for example, offer a reasonable explanation for the hemorrhagic areas often localized linearly along and near the junction of the intercostal tissues and the ribs as commonly seen and described by those familiar with blast-produced pathology.

Pressure differentials. Before turning to the biologic response to "short" and "long" duration overpressures rising to a maximum in different times, it is instructive to employ simple models to aid in visualizing certain qualitative relationships between environmental pressures external to an animal and those that might be expected internally in the gaseous and fluid phases of the lung at the alveolar level.

Consider FIGURE 1 which diagrammatically represents the trunk of an animal with the thorax above and the abdomen below. The trachea is shown, with a constriction representing the bronchiolar resistance to air flow, leading to a "box" representing the gaseous phase of the lung. Protruding into the gaseous phase, another "box" is shown representing the fluid phase of the thorax, including the vascular components. The latter communicates with the vascular elements below the diaphragm also shown as a "box" in the abdominal region.

The lower portion of FIGURE 1 represents a situation in which the environmental (external) pressure is assumed to rise slowly and to a modest degree. Under such circumstances, there is time for air to flow through the airways into the alveoli of the lungs at a rate which keeps the internal gaseous pressures increasing apace with those in the environment and liquid phases of the abdomen and thorax. If the pressures are

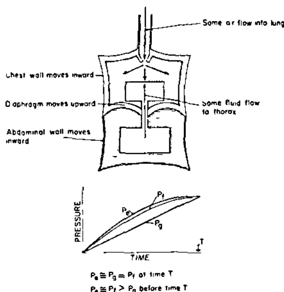


FIG. 2.—Diagram of model response to "slowly" rising overpressures to which "protective" response is effective.

not too high and prolonged, there would be no hazard.

FIGURE 2 *shows a faster rate of pressure rise* which does not allow time for gas to flow through the small airways into the alveoli in sufficient quantity and the rise in internal gaseous *pressure lags below the external and* liquid pressures. There results some movement of liquid into the chest, a compression of the abdomen and thorax, elevation of the diaphragm and a *decrease in thoracic gas volume*. As a consequence of the latter, particularly, the gaseous pressure in the thorax will rise and reach the level of the external pressure at some time, *T*, without development of serious events, providing the rise of the external pressure is not too high.

In FIGURE 3, a more rapid and higher pressure rise was assumed which, even after sharp maximal inward movement of the perimeters of the thorax, results in external and liquid pressures well above those in the gaseous portions of the lungs. Under such circumstances, blood moves toward the regions of lower pressure (squeeze syndrome), and rupture of the pulmonary vessels and lung hemorrhage results.

FIGURE 4 diagrammatically represents the results of a sudden, almost instantaneous rise in environmental pressure of relatively short du-

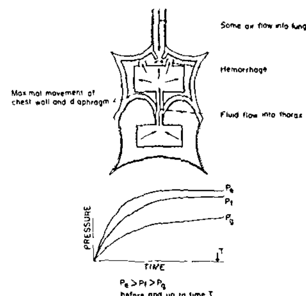


Fig 3—Diagram of model response to moderately "fast"-rising overpressures to which "protective" response is inadequate

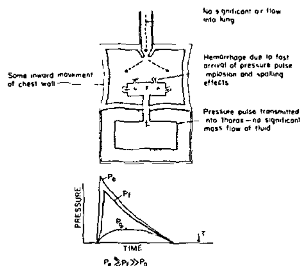


Fig 4—Diagram of model response to "fast"-rising overpressures of "short" duration

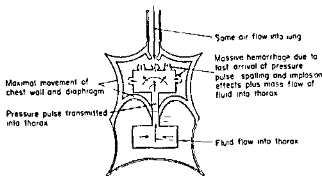
ration There is hardly time for significant compensation through compression of the thorax and air flow into the lung nor for movement of liquid into the chest The main effects here are due to the fast arrival of pressure pulses or shock waves which are transmitted through the chest wall to the liquid phase of the lung before an equalizing pressure pulse can be transmitted through the air columns of the pulmonary airways (sound travels faster in water than in air). Lung damage and hemorrhage results from the consequent pressure di- ferentials and probably from implosion an spalling effects discussed previously In cas the walls between the alveoli and the delicat pulmonary veins are ruptured, it is possible fo aveolar air to enter the vascular system durin the time of trauma and subsequently with eac respiratory cycle

Finally, in Figure 5, there is shown diagram matically a rapid rise in external pressure a in Figure 4, but the overpressure is sustained So in addition to the sharp, transient initia pressure differentials, implosion and spallin effects, there can be maximal compression o the chest and abdominal wall, elevation of th diaphragm and movement of liquid into th thorax All of these combine to produce massiv *pulmonary hemorrhage and other equally dan*gerous sequelae

Three other factors may play a role in this picture *(1) variations in the rising phase of* the pressure pulse which may involve "slow" or "fast" stepwise or sawtooth increases in pressure, *(2)* multiple loading from oscillating pressures[50] which can be related to resonance of different portions and organs of the body[18, 43] and (3) events which may transpire if the overpressure duration is sufficiently prolonged In the latter case, there will come a time when enough air has entered the chest to raise the density of the alveolar gas to that in the environment After this moment, the animal is "cocked" for decompression-like pathology, and damage may result if the falling phase of the pressure is of sufficient magnitude and rapidity Too, it is possible that gaseous supersaturation of the pulmonary capillary blood can occur during the time high alveolar pressures exist, in which case a sudden fall of pressure may then result in *intra-arterial* formation of gaseous emboli

BIOLOGIC RESPONSE

Attention will now be directed to the gross biologic response to blast-produced variations in environmental pressures The available data indicate that mammalian material in general (a) is less likely to be damaged by overpressures of "short" duration compared with those of "long" duration and (b) is more tolerant



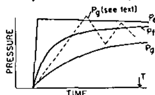


FIG 5—Diagram of model response to "fast"-rising overpressures of "long" duration The dotted line represents possible oscillations in the pressure of the gaseous phase of the lung

to "slowly" rising overpressures than to those developing almost instantaneously

Overpressures of "Short" Duration

For example, Fisher, Krohn and Zuckerman[21, 22] in excellent studies using high explosives to produce "fast" rising pressure pulses from 1 to 3 msec in duration showed that the overpressures associated with 50 per cent mortality (P_{50}) in mice, guinea pigs, rabbits, monkeys and goats were near 27, 32, 55, 100 and 200 psi, respectively. The authors related the P_{50} data to the weight of the three smaller animal species by the equation

$$P_{50} = 0.24\, W^{2/3} + 23.7$$

P_{50} = local static overpressure in psi

W = body weight in grams

From this relation the P_{50} for the 60 and 80 Kg man was predicted to be 390 and 470 psi, respectively The same authors cited 12 human exposures to bombs dropped on British cities under circumstances wherein the pressure could be estimated One fatality occurred at 450 psi, but there were 10 survivors at pressures between 170 and 450 psi and one between 500 to 600 psi

Desaga[16] in Germany during the war noted 2 deaths among 13 men exposed in an open-topped concrete gun emplacement to blast from a high explosive bomb detonated close by Estimates of the overpressure which occurred in a corner where the fatally injured men were located were said to involve an incident overpressure of 57 psi which reflected to a maximum of 235 psi

The Overpressure-Duration Relationship

Many years ago Hooker[28] stated that the duration of an overpressure was important in animal studies of the effects of blast pressures produced by mortars and large naval rifles Subsequent investigators[9, 16, 46] agreed that both the magnitude of the overpressure and its duration were of significance in assessing the relation between pressure variation and biologic response

Desaga[16] determined the fatal conditions for dogs in terms of the maximal local static presures (P_{100}) and the durations of the overpressures produced using high explosives as noted in TABLE 2

In the case of mice, a fairly recent study by Celander et al[7] is of significance The results are summarized in TABLE 3

"Long"-Duration Overpressures

Because of the need for studies applicable to nuclear explosions, experiments have been conducted for the United States Atomic Energy Commission both in the field and in the laboratory. In 1953, at the Nevada Test Site severe, though nonfatal, pulmonary damage was noted

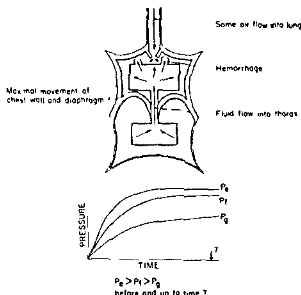


FIG 3—Diagram of model response to moderately "fast"-rising overpressures to which "protective" response is inadequate

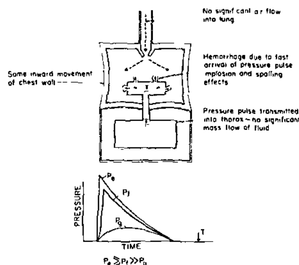


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Finally, in FIGURE 5, there is shown diagrammatically a rapid rise in external pressure as in FIGURE 4, but the overpressure is sustained. So in addition to the sharp, transient initial pressure differentials, implosion and spalling effects, there can be maximal compression of the chest and abdominal wall, elevation of the diaphragm and movement of liquid into the thorax All of these combine to produce massive pulmonary hemorrhage and other equally dangerous sequelae.

Three other factors may play a role in this picture (1) variations in the rising phase of the pressure pulse which may involve "slow" or "fast" stepwise or sawtooth increases in pressure, (2) multiple loading from oscillating pressures[50] which can be related to resonance of different portions and organs of the body[18, 43] and (3) events which may transpire if the overpressure duration is sufficiently prolonged In the latter case, there will come a time when enough air has entered the chest to raise the density of the alveolar gas to that in the environment After this moment, the animal is "cocked" for decompression-like pathology, and damage may result if the falling phase of the pressure is of sufficient magnitude and rapidity Too, it is possible that gaseous supersaturation of the pulmonary capillary blood can occur during the time high alveolar pressures exist, in which case a sudden fall of pressure may then result in *intra-arterial* formation of gaseous emboli

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insufficient data to establish any generalized relationships among the several species of animals which might also include man

The mammal exhibits much higher tolerance to "*slowly*" *rising* overpressures which fact is in sharp contrast to the response noted with "fast"-rising overpressures. For example, in a study using overpressures from 5 to 20 seconds duration having times to P_{max} which varied from about 30 to 160 msec., there was *no mortality* observed in dogs even though the overpressures involved were as high as 170 psi.[40a] The lung hemorrhages found were slight. Actually, the latter, unlike the more spotty and often diffuse damage noted with "fast"-rising overpressures, were almost entirely limited to the inferior margins of the lungs lying in the costophrenic sinuses. Apparently, the lungs were compressed between the inward-moving thoracic wall and the rising diaphragm due to implosion of the body wall causing narrow, wedge-shaped areas of hemorrhage along the caudal borders. Somewhat similar lesions have been described previously by Zuckerman[55, 56] in animals exposed "close" to small high explosive charges and explosions of hydrogen-oxygen mixtures in balloons. Osborn[35, 36] also emphasized the occurrence of costophrenic lung lesions from nonpenetrating trauma to the lower thoracic borders along with damage to the liver and spleen often associated with such cases. This emphasizes the utility of chest x-rays in thoracic trauma, which if they reveal marginal wedge-shaped opacities, should alert the physician to the possibility of abdominal pathology and the frequent need for early surgery.

Pathophysiologic Observations

Even though the pathology associated with exposure to blast-produced overpressures has been well documented[3, 9, 16, 28, 36, 40, 44, 50, 55, 56] and available pathophysiologic data have been discussed in an excellent recent *review* by Clemedson,[10] there remains a difference of opinion concerning the biophysical mechanisms at play along with interpretation of the events which lead to death.

A. Conditions of Exposure

Some of the earlier experiments using animals exposed to high explosive-produced blast ("fast"-rising, "short"-duration overpressures) are illuminating as indicators of significant factors in the etiology of blast pathology. For example, if an animal is shielded from an otherwise fatal explosive charge by a steel box from which the head protrudes, there is no detectable damage[3, 31, 55, 56] providing the head and neck are padded to avoid violent contact with the steel wall of the box.[31, 55, 56] This is so, even if a tracheotomy tube is attached to a funnel facing the charge,[3] indicating that the propagation of the blast overpressures down the respiratory tree is not of primary significance. Other measures for protecting the trunk of the animal from the "blow" of the blast wave also give protection as illustrated by such things as a rigid plaster of Paris cover and appropriate padding with sponge rubber, but not a thin plaster bandage applied to the chest and abdomen to avoid overdistention of the thorax.[3, 16, 31, 55, 56] Such observations suggest that it is the impact of the blast wave and overpressure against the body wall that is critical[3, 55] and not the negative phase of the pressure pulse. This view is also supported by the protection offered by experimental pneumothorax which if unilateral or bilateral offers considerable *protection to the lung on the side of the pneumothorax*.[3, 16]

Animals immersed hind feet first in water up to the diaphragm and exposed to an underwater charge show only abdominal pathology. When immersion of the abdomen and thorax is arranged, there is abdominal damage and also pulmonary lesions *plus* signs of central nervous system damage.[3] These facts and those above, along with electrocardiographic signs of anoxic cardiac disturbances, suggest that gaseous emboli arising *in the chest during or subsequent* to the blast and migrating via the circulation to the heart and central nervous system might be one important pathophysiologic event that could well prove fatal of itself.

B. Causes of death

Air emboli, hemorrhage and edema. Air emboli have been visualized by many investiga-

TABLE 2 —*Pressure-Duration Relationship for Near 100 Per Cent Mortality in Dogs Exposed to Sharp-rising, "Short"-Duration High Explosive Blast (after Desaga[16])*

Maximum Static Overpressure psi	Overpressure Duration msec.
216	1 6
218	1 6
125	4 1
85	8 6
79	10 3
76	11 8

Note Animals, lying on their sides with backs to the explosive, were exposed on level terrain to hemispherically molded charges detonated on the ground

TABLE 3 —*Pressure-Duration Relationships for the Indicated Mortality in Mice Exposed in a Shock Tube to Sharp-rising, "Short"-Duration Overpressures (after Celander et al [7])*

Overpressure			Number Animals Exposed	Mortality %
Static psi	Reflected psi	Duration msec		
15	43	4 4	18	33
		1.9	10	20
		0 15 ± 20%	10	0
19	59	4.6	10	100
		1.9	10	50
		0 15 ± 20%	10	10
24	75	4 7	10	100
		2 0	15	87
		0 15 ± 20%	15	73
29	100	5 0	6	100
		2 1	15	93
		0 25 ± 20%	15	80

Note Animals, inside loosely woven bags placed on the floor of the shock tube, were exposed nose-onto the advancing pressure pulse

in dogs exposed to nuclear-produced overpressures ranging from 12 to 25 psi in magnitude and enduring for from about 500 to almost 800 msec.[50] The findings also indicated that the rate of pressure rise was of importance. Animals tolerate "slowly"-rising overpressures of long duration much better than they do those that rise rapidly in a single or double step as the following paragraphs illustrate.

Using a shock tube in the laboratory, mortality curves were determined by Richmond for four species of animals exposed side-on against a metal plate closing a shock tube to "*instantaneously*" *rising* overpressures of 6–8 msec duration The reflected pressures required for 50 per cent mortality (P_{50}) were about 30, 33, 37 and 39 psi for mice, rabbits, guinea pigs and rats, respectively.[50a] Very recently similar experiments with dogs were completed by Richmond[1] for overpressures enduring for 400 msec. The P_{50} reflected overpressure was 48 psi A regression curve fit to these data relating the P_{50} pressure to body weight is as follows

$P_{50} = 26.03\ W^{[illegible]}$
P_{50} = reflected overpressure in psi
W = body weight in grams

The reader will appreciate that there is very little dependency in body weight for exposures in circumstances wherein the animal is enveloped by an incident overpressure and almost immediately thereafter by its reflection Solving the above equation for the mammal weighing 60 and 80 Kg gives P_{50}'s of 49 and 50 psi, respectively, as a *tentative* estimate for man for "*fast*"-*rising*, "*long*"-*duration* reflected overpressures

In instances in which the rising portion of a pressure pulse consists of *two* steps, as in the case when animals are mounted at various distances from a reflecting surface, tolerance to overpressure increases For example, guinea pigs exposed against 1, 2, 3, 6 and 12 inches from the end-plate closing a shock tube show P_{50}'s of approximately 37, 41, 48, 53, 59 and 57 psi, respectively,[50a] where the pressure is the reflected pressures of "long"-duration (*6 to 8* seconds) Against the end-plate, the animal "sees" the incident and reflected waves almost instantaneously To the contrary, at locations away from the reflecting surface, the animal is exposed in sequence to the incident wave and at a finite time later—1 4 msec. for *the locations* at 1 foot—to the higher reflected overpressure Thus, the animal is extraordinarily sensitive to any degrading of the rate of rise of the overpressure and great care is required in interpreting the quantitative meaning of exposures to phenomena of this character As yet, there are

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B Causes of death

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tors on the arterial side of the circulation in dogs,[1, 3, 16, 44, 50a] rabbits,[1, 12, 50a] guinea pigs,[50a] rats[1] and man[44] exposed to blast overpressures. Studies with experimental air emboli have demonstrated that (a) injected air migrates to the most superior portions of the vascular system and the consequence to the animal is largely influenced by body position, and (b) the detailed anatomy involved and blood flow as well as the amount of intravascular gas are of considerable significance. There is an element of chance in certain experiments wherein a single air embolus may migrate into a large coronary vessel or vital area of the central nervous system with death resulting in a few minutes. Almost immediate signs of severe and progressive anoxia of the myocardium demonstrable with the electrocardiogram are seen, both in blast and experimental arterial air embolism, with death often following fibrillation that develops fairly quickly.

In contrast, animals severely injured from blast do not die immediately but apparently suffer various degrees of broncho-venous or alveolar-venous fistulas through which air may enter the pulmonary venous circulation with each respiratory cycle "pumping" additional air into the circulation. The result can be massive air embolism involving the heart, brain and other organs. Further, it is important to recognize that under circumstances of moderate lung damage, pulmonary vasoconstriction and hemorrhage—particularly the latter—can act protectively in that the fluid "seals" the alveolar-venous or bronchovenous fistulas. An animal so situated may escape immediate death from emboli, but then faces the dangers from continued hemorrhage and edema. To these two factors, which in themselves embarrass the pulmonary circulation, are added the additional effects of transient circulatory arrest,[16, 31] bradycardia,[3, 9, 10, 16] lower systemic arterial pressure,[3, 9, 13, 28] vasoconstriction,[6, 8, 10] followed by vasodilatation,[6] in-



FIG 6—Heart of fatally injured dog exposed in a shock tube to a reflected pressure of 40 psi enduring for 6 to 8 seconds. Note air emboli in the larger and smaller cardiac arteries.

creased venous pressure,[32] and nonfatal, acute insult to the heart, signs of which are known to persist[9, 16, 32] in some cases for days in animals[3, 9, 10, 16] and man[2, 16, 32]

FIGURE 6 shows a photograph of the heart of an animal weighing 16 8 Kg exposed side-on against a reflecting surface in a shock tube to "fast"-rising, "long"-duration overpressure The reflected pressure was 40 psi. Frank blood was noted coming from the nares and mouth Air emboli were observed in the arteries of the heart, as can be seen in FIGURE 6, and in the brain There was extensive pulmonary hemorrhage The frontal sinus and larynx were also hemorrhagic Both eardrums were ruptured

Another animal, weighing 14 8 Kg and similarly exposed to a "fast"-rising overpressure reflecting to 39 psi, also died with similar findings FIGURE 7 shows an enlarged photograph of the coronary vessels containing copious amounts of air in different branches of the coronary arteries

Additional observations bearing upon the existence of air emboli in animals exposed to blast include reports that· (a) electrocardiographic evidence of hypoxia and myocardial damage, which appear after exposure of animals to blast, can be reversed by use of a compression chamber;[4, 12] (b) animals, otherwise fatally injured by blast, can be saved but not invariably so by immediate compression,[4, 12] (c) the electrocardiographic changes following arterial air emboli are similar in man[16] and animals[3, 9, 12, 19, 32, 48] to the findings after exposure to blast; and (d) *compression markedly improves the electrocardiographic signs of coronary malfunction* produced by experimental arterial air emboli[3]

Heart In addition to damage to the heart directly from coronary air embolism and in-



FIG 7—Enlarged view of coronary vessels of a dog fatally injured by a shock tube-produced, reflected overpressure of 39 psi enduring for 6 to 8 seconds Note gas bubbles in the larger coronary arteries and apparent breaks in the blood columns of the smaller vessels due to displacement of blood by intravascular gas



FIG 8—Enlarged view of bruised and hemorrhagic area of the myocardium of a dog fatally injured by a "fast"-rising shock tube-produced overpressure of 40 psi (reflected) enduring for 6 to 8 seconds Massive arterial air embolism is also easily seen

directly from hemorrhage, edema and the subsequent anoxia and dilatation, there apparently occurs significant bruising of the heart sometimes noted under the term "commotio cordis"[3, 10, 16, 30] Internal and external hemorrhagic areas and bruising of the epicardium and myocardium do occur but rarely rupture They are said to account for only a small percentage of early fatalities[3, 16] FIGURE 8 shows a bruised area of the myocardium in a fatally injured dog exposed in a shock tube to a reflected pressure of 40 psi FIGURE 9, a photograph of the lungs of a nonfatally injured dog exposed to 24 psi reflected overpressure, is of interest because it clearly illustrates the type of lung pathology noted at the contact between heart and lungs The damage which can occur at air-fluid junctions due to differences in tissue density has been mentioned earlier This, of course, can damage both the heart and the lung In the former case, the pathologic signs and the immediate and persistent electrocardiographic findings can be, in part, a reflection of such injury and may involve early fatality or delayed effects in surviving animals It is difficult, if not impossible under certain specific circumstances, to establish whether the critical etiologic factors involve air emboli or commotio cordis as the single cause of death or malfunction, if indeed, such is the case

Central nervous system. Various signs of focal damage to the central nervous system have been described involving lethargy and paralysis of the posterior extremities by Hooker,[29] ataxia,[1] and a variety of other symptoms observed by Benzinger in classic form in water blast where the animals' heads were not immersed[3], e g, the head was the superior portion of the body Krohn et al[31] reported delayed electroencephalographic signs of circulatory disturbances or cerebral hypoxia

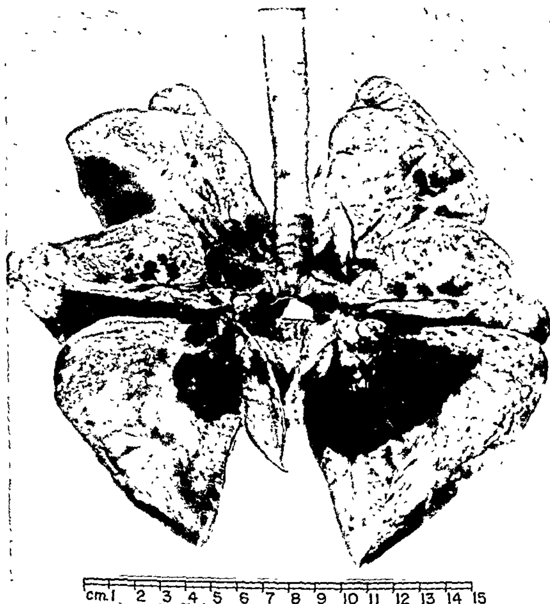


Fig 9—Ventral view of lungs of a dog non-fatally injured by a sharp-rising shock tube-produced overpressure of 21 psi (reflected) of 6 to 8 seconds duration Note the area of hemorrhage in the lungs that were in contact with the heart

in monkeys exposed to blast From what is known today, air embolic insult to the central nervous system offers adequate explanation of nervous symptoms and pathology,[3, 8, 12, 16, 19, 24, 41, 48] and it is doubtful that the mechanism involving transmission of hydrostatic shock waves from the body fluids into the closed cranium described by Young[54] plays a significant role It is conceivable that air embolism to vital nervous centers, particularly in animals exposed to blast with the head uppermost can contribute to early death as well as to delayed focal signs

General Though no precise explanations of the causes of death and the etiologic events applicable to blast can be set forth, it appears clear that (a) direct damage to the heart can, but rarely causes death immediately, (b) coronary air emboli can and do produce almost immediate death, but typically the fatally injured animal expires in from 2 to 10 minutes, (c) suffocation due to hemorrhage

and edema with concomitant hypoxia probably produces fatality in a somewhat longer period, though it is not common for animals who survive 15 to 20 minutes to succumb later; (d) malfunction of vital centers of the central nervous system may be a factor in early death from massive air embolism which is to be distinguished from damage due to frank physical head trauma; and lastly (e) the animal escaping early death may face the challenge of delayed complications from postconcussion pneumonia, perforations of the abdominal viscera, peritonitis, prolonged coronary signs with possible infarction and persistent local areas of damage in the central nervous system

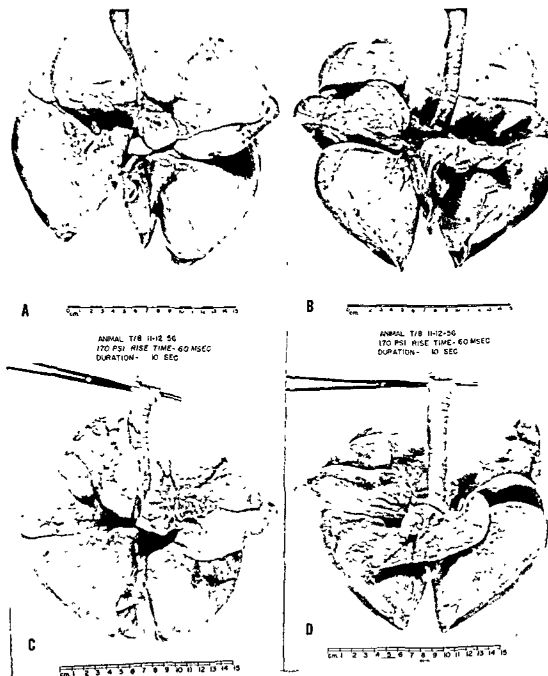


FIG 10—(A and B) Dorsal and ventral views, respectively, of lungs of a dog exposed nonfatally to a shock tube-produced, 10 second duration overpressure developing in *60 msec*, *to* a maximum of 170 psi Note marginal hemorrhagic lesions and absence of generalized areas of damage (C and D) Dorsal and ventral views, respectively, of normal lungs of a dog

"Slowly" Rising Overpressures

In a previous section, the marginal lung emorrhages commonly seen in animals exosed to "slowly" rising overpressures of long uration were mentioned FIGURE 10A AND B re photographs of the dorsal and ventral iews, respectively, of the lungs of an animal subjected to a "slowly" rising overpressure of 170 psi. FIGURE 10C AND D show normal lungs for comparison In contrast, the massive lung hemorrhages produced by a "fast"-rising overpressure are shown in FIGURE 11A which depicts the lungs of an animal fatally injured by a "fast"-rising overpressure reflect-

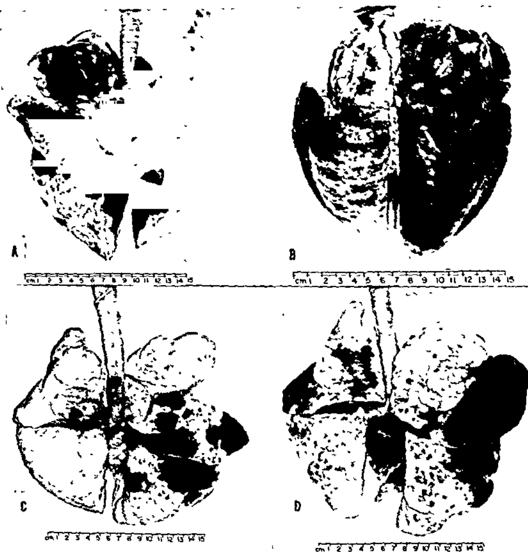


FIG 11 —(A) Ventral view of lungs of a dog fatally injured in a shock tube by a 6 to 8 second duration, reflected overpressure of 44 psi which developed almost instantaneously Note massive areas of hemorrhage (B) Dorsal view of lungs of pig fatally injured at the Nevada Test Site by nuclear-produced blast Overpressures were not measured at the location of exposure at the bottom of a stairway leading to an underground shelter Note the rib markings, massive hemorrhages and atelectasis of the left upper lobes (C) Dorsal view of lungs of a dog surviving impact of a 0 4 pound missile travelling 103 feet per second Note the isolated, somewhat discrete, unilateral areas of hemorrhage which occurred on the side of impact (D) Dorsal view of lung of a dog fatally injured by impact of a 0 4 pound missile travelling 207 feet per second Note bilateral location of the hemorrhage most severe on the side of impact (Data courtesy V. C Goldizen)

ing to a maximum of 44 psi FIGURE 11B, a *photograph of the lungs of a pig fatally* injured at the Nevada Test Site, is shown to illustrate rib markings, massive hemorrhage and atelectasis of one lobe.

D Local trauma

The unilateral and bilateral lung hemorrhage occurring from unilateral impact of nonpenetrating missiles is illustrated in FIGURE 11C AND D, respectively. The lungs in FIGURE 11C show those from an animal struck, nonfatally, in the midlateral, right thoracic region with a 0 4 pound missile 2 75 inches in diameter travelling at 103 feet per second FIGURE 11D, also from an animal hit in the right lateral thorax with a 0 4 pound missile, demonstrates bilateral hemorrhages found at necropsy after death which occurred in a few minutes following missile impact In such severely injured animals there appear electrocardiographic signs of hypoxia, and death from cardiac fibrillation [27]

Notes on Symptoms and Therapy (Prophylaxis)

Initially, it is well *to point out* (King and Curtis[29]) that prevention should be practiced whenever possible, e g , the use of abutments, shelters, measures to reduce the rate of pressure rise, sharp pressure reflections, missile production and their impact with a biologic target, displacement and subsequent violent deceleration, and the use of energy-absorbing garments covering the chest and trunk

A Position

Any symptomatic human case in which exposure to blast is suspected—particularly with ruptured tympanic membranes, or if, without other external signs of injury, bloody foam and frank blood are observed running from the nose and mouth—should be placed immediately in the left lateral or midway between the prone and left lateral position with the head lowered and kept there for several hours This is the position of choice to minimize the effects of intravascular air emboli by attempting to avoid migration of air *into the coronary* and cerebral vessels [19] The head-down position will also aid drainage of the pulmonary airways However, mechanical suction in appropriate instances should be used aggressively, along with detergent aerosol inhalations in stubborn cases, for the presence of foamy fluids *in the trachial and bronchial passages* seriously impedes air exchange If later on, signs of increased venous pressure develop, slight elevation of the head and upper trunk may be help*ful* [32]

B The Value of Rest

Complete rest is mandatory, for it is essential to reduce the work load on the embarrassed heart, lungs and circulation to avoid further pulmonary hemorrhage and edema and heart failure There exists the possibility of dislodging blood clots "sealing" damaged vessels and broncho-venous or alveolar-venous fistulas, an event to be avoided at all costs Reoccurrence of bleeding into the lung has been observed up to five days after exposure[33] *and has accompanied other signs in delayed* fatalities

C Pressurization

The use of therapeutic pressurization of the whole body up to 4 to 6 atmospheres, effective in experimental air embolism and suggested as a means of human therapy in blast, would have to be used almost immediately to be of value *in the majority of critical injuries* Consequently, such therapy is only of academic interest

Any therapy involving intrapulmonary application of inspiratory positive pressure is contraindicated

D Analgesics, Sedatives and Narcotics

Patients subjected to blast may exhibit various levels of awareness from normal mental alertness through amnesias to frank unconsciousness There may be various grades of motor activity from lethargy through flaccid and spastic paralysis to violent convulsions Pain may be present and severe. Whatever the signs, care in the use of narcotics, sedatives and analgesics must be exercised In blast injury involving damage to the lungs and heart, coughing and increased motor activity must be controlled definitely for the first few hours

and for days if necessary, since frank bleeding may continue for 48 hours,[26] and periodic hemoptysis for as long as 7 to 10 days has been reported Morphine and atropine or other narcotics are recommended if necessary to control pain, secretions and restlessness providing less potent measures are ineffective Although sedation is important to provide rest, it should not mask signs of (a) existing or progressive damage to the central nervous system (head trauma often also is involved), (b) persistent *chest pain which may aid the diagnosis of* early myocardial infarction and (c) abdominal injury requiring surgical intervention All surgical procedures should be avoided whenever possible for at least 24 hours because of the poor early tolerance to general anesthesia exhibited by victims of blast [16]

E Oxygen Therapy

Oxygen therapy has been recommended widely in blast casualties,[10, 16 24, 29, 32] and has *been reported to be effective in air embolism* [4 20] The elimination of any increase in pulmonary vascular resistance due to hypoxia is most desirable Even so, careful administration of oxygen is essential to relieve (1) cyanosis or hypoxia in cases with low hemoglobin from hemorrhage which sometimes precludes the development of cyanosis, (2) persistent chest pain and electrocardiographic anomalies and (3) it may be indicated in selected cases with signs of central nervous system damage However, *careful control, involving use of* reduced concentrations in some cases and discontinuance if any signs of recurrence of pulmonary hemorrhage develop, should be maintained When available and when the indications for oxygen therapy exist, the use of helium-oxygen mixtures to reduce the work of breathing certainly is indicated

F Intravenous Medications and Digitilization

Because of damage to the thoracic organs, a lowered blood pressure almost always accompanies severe blast injury This may be confused with the ordinary shock syndrome often accompanying trauma, when in reality the low systemic blood pressure stems from (a) a myocardium insulted by bruising, hemorrhage and insufficiencies of the circulation which are sequelae of nonfatal air embolism, (b) pulmonary emphysema, hemorrhage and edema serving to increase the work load on the right heart and interfere with efficient oxygenation of the blood and (c) reflex lowering of the peripheral blood pressure initiated through the vagal endings situated in the damaged lungs, which is interpreted to be a protective mechanism serving to minimize the work load of the left heart.[3] Such events contraindicate the use of intravenous fluids, plasma or blood unless absolutely necessary because of hemorrhage from lacerations or other wounds or because the systemic pressure falls definitely to dangerous levels Even when required, intravenous fluids must be used with caution, for there is danger of overloading an already damaged heart and pulmonary circulation, and often difficulties with electrolyte balance occur due to malfunction of the renal system (Damage to the kidneys is not uncommon in blast *cases* [5])

With fluids given intravenously even without intravenous medication, acute heart failure and marked pulmonary edema can develop suddenly in blast cases [32] Instances of fulminating cardiac insufficiency have been described as long as five days after injury, and some cases show an elevated venous pressure for which venisection and cardiac glucosides have been employed effectively [32] The use of intravenous digitalization in such instances is generally indicated and may prove life saving Though digitalization has been recommended[16 32] for the true cardiac insufficiency which is one of the fundamental consequences of blast injury, instances of its use are not fully defined in the literature

Caffeine administered systemically at first in large doses as a stimulant and diuretic and later by mouth in coffee has proven useful in treating blast casualties, providing the dose in the late afternoon and evening is cut back so as not to interfere with sleep which is commonly disturbed in such cases [16]

Intravenous alcohol slowly injected as a 30 per cent solution in doses up to 30 to 40 cc has been recommended for its euphoric and

mild anesthetic effects Alcohol also acts as diuretic and a dilator of the coronary and peripheral vessels, all additional desirable effects

G Pneumothorax, Thoracentesis and Antibiotics

Therapeutic pneumothorax has been suggested[30] as a "last-ditch"[16] measure to control continued pulmonary hemorrhage in stubborn cases that have not responded to conservative measures

Thoracentesis to remove pleural fluid may be most helpful in patients with markedly embarrassed pulmonary exchange, but should be performed early only in case of dire necessity to avoid possible resumption of hemorrhage that might accompany expansion of the lung For this reason even delayed thoracentesis should be approached and used with great care

Apparent enlargement of the heart may occur because of increased pulmonary pressure, impending or existing heart failure or because of pericardial effusions[27] and/or early or delayed hemorrhage into the pericardium[32] In the case of actual or threatened heart failure with elevated venous pressure, rapid digitalization and venesection should be considered Enlargement due to fluid, however, can progress to tamponade and decompression of the pericardial sac is indicated

Consolidations—scattered, irregular, isolated or confluent—may be observed in lungs of blast victims and often resemble those noted in broncho or lobar pneumonia by x-ray and physical examination Without complication these blast-produced areas of hemorrhage clear remarkably well in man and animals However, infections in the human case have been reported as frequent complications[37] and when present should be treated as in pneumonia. All cases with pneumothorax or hemothorax arising from rupture of the surface of the lung are potentially contaminated and antibiotics should be employed routinely to avoid development of empyema.

H Anesthesia

The poor tolerance of blast cases to general anesthesia should be emphasized Unless there is a real urgency surgery should be avoided for at least 24 to 48 hours[16, 29, 32, 37, 41] and in some instances longer.

One clinical observation noted in blast casualties by Roberts[42] deserves mention as a guide to surgeons and anesthesiologists Some blast cases show minute punctiform hemorrhages in the skin of the abdomen and chest which were not readily apparent When observed it should be assumed that the patient is suffering from blast and treated appropriately until proved otherwise

The classic pathognomic signs of air embolism might also be helpful to the clinician. These are

1 Ophthalmoscopic detection of air embolism directly and immediately in the retinal vessels as streaming bubbles or pale silvery sections representing columns of air, or indirectly and later as pallor of the retina which may be noted for several days and be associated with diminution of visual acuity[15, 30, 47, 53]

2 Liebermeister's sign consisting of sharply defined areas of pallor in the tongue depending upon the lingual arteries or their branches involved in air embolism[30]

3 Marbling of the skin, a dermal manifestation due to embolism of the skin vessels especially over those portions of the body superiorly located at the time emboli occurred[19]

4 "Air bleeding" that has been observed from skin incisions made over the most superior portions of the body[46]

5 Roentgenologic demonstration of air in the cerebral vessels of little value except as a means of postmortem diagnosis[*]

I General

The multiple nature of blast-produced damage from overpressure, flying debris and injuries as a consequence of displacement is amply illustrated by war casualty experiences[38] and by medical reports of the Texas City Disaster[5, 45] The proper use of heat, fluids, plasma, blood and vasopressors to control traumatic and hemorrhagic shock, along with the requirements for emergency surgery is, of course, most important However, among the secondary and tertiary blast casualties will be those who have survived the immediate hazards, but who will exhibit various degrees of primary blast injuries to the thoracic and abdominal organs. These pose an important problem to the medical profession in diagnosis, treatment and careful follow-on care.

While it is unfortunate that the pathophysiologic nature of primary blast damage portends early fatality for many individuals exposed to higher overpressures, both incident and reflected, it is at the same time fortunate that the hazards from overpressure do not extend farther from an explosion than they do The properly informed and alert practitioner today is in a much more favorable position than in the past because the understanding of the basic lesions due to overpressure is currently more advanced. Certainly in the future, cases which previously would have been lost early, will survive because of a more enlightened and sophisticated approach to therapy

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decreased by approximately .10 pH during the first five minutes of recovery after heavy exercise, while the ventilation dropped from approximately 75 L to 28 L.[27] During this same period, the arterial P_{CO_2} decreased progressively from 40 mm Hg during exercise to 33 mm. Hg by the fifth minute of recovery. (These are average values for eight observations at each level of recovery.) It is readily apparent from these experimental observations that the arterial pH *alone* is not the regulator of respiration during exercise and recovery Its possible relationship to exercise ventilation as one of several factors acting jointly will be considered further.

The sensitivity of the respiratory center to changes in pH has not been fully assayed over its physiologic range, nor completely at any level, since at rest a decreased pH induced by the administration of ammonium chloride, HCl, or an increase in metabolic acids is associated with a decrease in P_{CO_2} as well as changes in other unmeasured factors Obviously, it is difficult to separate the effects of an increase in hydrogen ion per se from the various changes Such measurements as have been considered up to the present time indicate that pH levels have a relatively slight effect upon the ventilation In one study a decrease of .20 pH was associated with an increase of 3.1 L of ventilation,[7] while in another study a decrease of 07 pH was associated with an increase of only 0.10 L. ventilation.[6]

The multiple chemical factor theory The studies mentioned (above) do not provide an accurate estimation of the sensitivity of the respiratory center to changes in pH. In order to achieve such information the pH change must be induced while the P_{CO_2}, temperature and other variables remain constant. These and other important interrelationships of the chemical factors concerned with regulation of the ventilation have been stressed by Gray in the development of his "multiple factor theory."[16] He proposed the following stimulus equation, describing in an approximately quantitative manner the effect of the three chemical agents

$$VR = 0.22\, H^+ + 0.262\, P_{CO_2} + \frac{105}{100.088\, P_{O_2}} - 18$$

VR = the alveolar ventilation ratio (the alveolar ventilation during a test condition divided by the normal resting alveolar ventilation).

H^+ = the arterial hydrogen ion concentration in mμmoles per liter;

P_{CO_2} = the arterial CO_2 tension in mm Hg.

P_{O_2} = the arterial oxygen tension in minutes Hg

"This equation states that each of the three chemical agents, P_{CO_2}, H^+ and P_{O_2} exerts an independent effect on ventilation, and that the actual ventilation is the algebraic sum of the partial effects of all three. The 'sensitivity' of ventilation to each agent (i.e., the change in VR per unit change in concentration of the agent) is defined by the respective coefficients"[17] The interdependence of the variables is emphasized, i.e., a change in one of the chemical agents must be accompanied by a change in the other factors Gray concluded that the chemical factors alone could not completely explain the hyperpnea of exercise. First of all, he accepted the evidence that in moderate exercise neither P_{O_2}, P_{CO_2} nor pH are changed. Direct measurements of these agents in arterial blood during exercise are few and are of restricted range The available data indicate a slight increase in P_{CO_2} during moderate exercise, with a subsequent decline to below resting levels during severe exercise, persisting throughout recovery. While the pH may not decrease during light exercise, there is good evidence that it does so during moderate and severe exercise, remaining depressed for a variable time in the postexercise period These changes are shown in FIGURE 3 Furthermore, it has been considered that blood lactate does not rise during mild exercise This belief, largely based upon measurements obtained during recovery, has been challenged recently with measurements made during exercise in which an increase in lactate proportional to the relative severity of the exercise has been found in normal and abnormal subjects.[22] The demonstration by Huckabee of the mass action relationship of pyruvate and lactate, by which lactate may be altered without an implication of anaerobic metabolism,[19] has offered a rational

explanation for many of the apparently contradictory findings. This does not imply that liberation of lactic acid is synonomous with a decrease in pH, since lactic acid may react with buffers in the blood and body fluids without an appreciable change in pH. It does imply, however, that the ventilation equation given above may not be simplified critically by assuming that no change in metabolic acid-base balance occurs in mild or moderate exercise. The concept of the multiple factor control of the ventilation is important, a potent research tool. It seems obvious that more direct measurements of the three major chemical factors at many levels of exercise, including minute-by-minute studies, are urgently indicated, as are data on the sensitivity coefficients obtained under rigidly controlled circumstances.

The possibility still remains that other products of muscle metabolism may play a role in the hyperpnea of exercise. These could include potassium, phosphate, and altered enzyme systems among others that could affect the respiration centrally or reflexly. Direct measurements during exercise, both in arterial and venous blood should clarify the problem.

Neural Mechanisms

1 *Extremity reflexes:* Since the considerations, rightly or wrongly, have changed from the exclusively chemical concepts of ventilatory control, renewed attention has been directed to the possibility of a dominant neural factor. Harrison et al., in 1932, demonstrated in the dog that passive motion of a disarticulated limb, completely devoid of vascular connection with the body, resulted in a small but definite increase in ventilation[20] The hyperpnea was abolished by sectioning the sciatic nerve. These observations have more recently been confirmed and extended by other investigators It is important to realize, as pointed out by Gray, that the potential sensitivity of the mechanism to these stimuli would be greatly underestimated if the P_{CO_2} is lowered and the pH increased by the resulting hyperpnea Assuming that the exercise was truly passive, it is concluded that such a stimulus, capable of increasing the ventilation by 20 per cent without an increase in metabolism, could produce an increase in ventilation of 500 per cent during active exercise However, it has not been shown that the "passive" exercise occurred without metabolic effect. Moreover, it has not been proved that proprioception is the responsible modality. The time course of the ventilation during exercise and recovery in itself is evidence that proprioception occurs as a less dominant factor. Accordingly, it seems hardly credible that proprioceptive impulses could play an important role in the hyperpnea of the postexercise recovery period which may persist for upward of 10 minutes after severe exercise. Furthermore, there is evidence as to the presence of potent receptors in the extremities of experimental animals that are capable of stimulating the ventilation reflexly. For example, in animals whose extremities are entirely perfused by the circulation of a "donor," the regression of ventilation on oxygen consumption is similar to that of the same intact animal during exercise. The metabolic activity in the perfused extremity may be increased both by electrical stimulation of the nerve or muscle and by the injections of 2–4 ditrophenol, the latter obviating the possibility of significant stimulation of proprioceptive impulses[23] These experiments seem to resolve most of the criticisms on the existence and relative potency of metabolically sensitive neuroreceptors in the extremities.

The carotid and aortic body reflexes. That the carotid and aortic body reflexes control to a *major* extent the ventilatory response to anoxemia is well established As mentioned previously, however, the arterial P_{O_2} probably does not decrease significantly during exercise in normal subjects, except at levels of extreme exhaustion. In addition, there is evidence that the carotid and aortic bodies are highly sensitive to temperature change[5] The potential importance of the temperature factor has probably been underestimated for the same reasons cited above in referring to the potential importance of the reflexes from the extremity, i e., failure to control the chemical factors while temperature is increased. In addition, it has been assumed that the time-course of the rectal temperature is representative of temperature fluctuations of the blood, although justification

for this assumption is not immediately apparent It would appear more likely that the temperature of the venous blood draining an extremity would rise acutely with the onset of exercise Once again, direct measurements of venous and arterial blood by suitably sensitive means during exercise and recovery are highly desirable.

An elevated temperature may increase respiration through various mechanisms in addition to the carotid and aortic body reflexes These include actions (1) upon the central nervous system, (2) upon the blood as a physiochemical system and (3) by peripheral reflex phenomena. Since the liberation of heat by working muscles fluctuates as the metabolic rate, and since the mechanisms of heat dissipation often may be impaired during circulatory insufficiency, a careful, continuous measurement of blood temperatures during exercise and recovery might well throw additional light on the mechanism accounting for the hyperventilation of exercise as found in patients with cardiopulmonary disease

Additional reflexes arising from pressure or volume receptors in the right heart or pulmonary vasculature have been considered of some importance in the production of hyperpnea of exercise. The experimental evidence at present is inadequate for the proper evaluation of these receptors, although recent studies seem to indicate clearly that the increased cardiac output of exercise is not associated with a proportionate increase in cardiac or pulmonary blood volume in normal subjects However, it is now known that the pulmonary artery systolic pressure tends to rise somewhat proportionately to the cardiac output. These reflexes could therefore serve as an additional stimulus and possibly become of greater importance in conditions such as mitral stenosis

In summary, there is evidence of various mechanisms by which the ventilation may be [illegible] ...rements of exer- [illegible] hat any [illegible] explain this phenomenon fully. On the contrary, there are present apparently both neural and humoral factors of varying importance. Some of these may well be relatively inactive at low levels of work but become dominant at higher levels. Other pathways may become important under certain pathologic conditions Many important areas of exploration remain as stimulant to further investigation.

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Section VI

EVALUATION OF PULMONARY PHYSIOLOGY

Physiologic Interpretations from History, Physical Signs and Roentgenography

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THE increasing use of laboratory procedures in the evaluation of pulmonary function has minimized, to some extent, the importance of the medical history and physical examination as routine measures It should be mentioned, however, in this day of the ascendancy of science in modern medicine, that much can be learned from a few well directed questions and certain pertinent observations. Often, these will obviate the need for more detailed and complicated studies, and such data may prove invaluable in the physiologic interpretations

The function of the lungs is concerned mainly *with delivering oxygen to and removing carbon* dioxide from the tissues This is accomplished through three main activities (1) ventilation, the movement of air in and out of the lungs, (2) alveolar-capillary exchange, or delivering air to the alveoli and across the pulmonary membrane into the blood; and (3) pulmonary circulation, or maintaining an adequate blood flow to the alveoli For normal function of the lungs, therefore, alveoli must receive sufficient oxygen in the inspired air, gas exchange must take place between the alveoli and the capillaries without difficulty, blood in adequate amounts must reach the lung and carbon dioxide must be carried from the tissues to the expired air To carry out these functions requires coordinated activity of the entire body Adequate ventilation depends on proper functioning of the diaphragm and the accessory muscles of respiration, a patent airway and normal elasticity of the pulmonary tissues. Inspiration results from voluntary effort but expiration is dependent upon the elastic recoil of the lung and the Hering-Breuer reflexes which carry inhibitory impulses to the respiratory center through the vagus when the lung is distended. The blood pH and the arterial carbon dioxide tension must be within normal limits as the respiratory center is stimulated reflexly by a drop in the pH or directly by a rise in the carbon dioxide The respiratory center must also be normally responsive to either vagal or chemical stimuli

Impairment of pulmonary function in chronic lung disease is due to a variety of causes, related basically to the amount and location of fibrosis, the degree of associated emphysema and the condition of the bronchial tree. The interplay of these various factors will be reflected in certain complaints and physical findings *Analysis of these signs and symptoms may* reveal the basic underlying pathologic and physiologic disturbance. In this respect, dyspnea, cough and expectoration may become significant manifestations.

The tracheobronchial tree has several functions conduction, or delivery of air into the alveoli, air-conditioning, with cleansing and humidification of the air as it passes over the mucosa, and drainage, through action of the ciliated epithelium Interference with any of these functions will produce symptoms and/or signs The basic disturbance in acute states, such as asthma, and frequently in chronic disease, such as emphysema, is obstruction of the airway due to one or more of the following factors: spasm of the smooth muscle of the bronchi and bronchioles, edema of the bronchial mucosa, and changes in the amount and character of the mucous secretion by the bronchial glands, with retention of this secretion. The clinical picture seen in these conditions reflects the disturbed physiology.

It will be the purpose of this chapter, therefore, to emphasize those aspects of the history and physical examination which may suggest the underlying disturbance of lung function

and to interpret them from a physiologic point of view

History

The history provides information of diagnostic and prognostic importance. It should be as complete as possible, emphasizing those aspects bearing on the pulmonary problem. Inquiry should be made not only of the present illness but also of occurrences in the past and in the family history which may have a relation to the present complaints. It should begin with a review of the work history, seeking to uncover any recurrent exposure to harmful or irritating agents. The exact type of work, the length of time employed and the work environment should be recorded in chronologic order. Specific search should be made for exposure to silica, asbestos and beryllium, which cause known disabling pneumoconioses. Such occupations as mining, driving of tunnels, highway construction and stone cutting entail a definite silica hazard, and should be noted. Industries concerned with the processing of minerals, as in smelting and refining of ore and the industrial use of sand and gravel, and the manufacture and use of abrasives must be considered. A history of work as an arc-welder may be significant, as may exposure to fluorescent lights. Employment in certain geographic locations may suggest the possibility of fungus diseases, such as coccidioidomycosis and histoplasmosis. Work on a farm or with birds may pose the question of viral infections, such as psittacosis.

Inquiry should then be made as to previous respiratory symptoms, in order to judge the cause, nature and extent of existing pulmonary changes and to evaluate their role in favoring disability. A history of sinus disease and frequent head and chest colds is significant. Recurrent bronchitis may be the precursor of latent obstructive emphysema. The response of bronchitis to previous antibiotic therapy should be especially noted. Persistent dyspnea with a history of true allergic asthma may suggest the development of an appreciable degree of emphysema. Recurrent pneumonitis might suggest chronic disease, such as bronchiectasis. A past history of tuberculosis may be significant, particularly if pulmonary insufficiency is a factor, as dyspnea may be due to compensatory emphysema resulting from the fibrosis and retraction which characterize the healing process. Recent intense radiation therapy applied to the thorax may suggest radiation pneumonitis as the cause of dyspnea. Previous heart disease may very well suggest a cardiac origin for pulmonary insufficiency.

The chief complaint should be carefully established, as it will frequently indicate the line of questioning to be followed. If the patient is no longer employed, then the cause and date of work stoppage should be ascertained. If work stoppage occurred because of dyspnea, then this symptom should be considered in detail. The length of time dyspnea has been present, the rapidity of its development and its relation to effort must be considered. Dyspnea in varying degrees may be expected in 85 to 90 per cent of patients with demonstrable, disabling pneumoconiosis or emphysema. In these cases dyspnea is usually gradual in onset, shortness of breath on exertion being noticed several years prior to work stoppage. With increased severity, accentuated by bouts of intercurrent infection, lighter or easier employment is generally requested until work stoppage becomes mandatory. In certain cases the onset of dyspnea may be abrupt, suggesting some complication such as infection or spontaneous pneumothorax.

Dyspnea, as considered in the medical history is a subjective symptom which can best be defined as an awareness of the need for increased respiratory effort. It can be perceived and judged only by the patient. Many interrelated factors enter into the production of dyspnea, most of them manifested by changes in the function of the lungs which can be measured by our present pulmonary function tests. In some cases, however, it may not be possible to demonstrate significant changes from the normal by present means. Restrictive lung disease results from loss of functioning lung tissue with a static reduction of all components of the lung volumes. Dyspnea in the presence of a proportionately greater reduction of the vital capacity than the maximum breathing capacity is characteristic of this state of affairs and is seen in such clinical conditions as asbes-

tosis and sarcoidosis. Although the vital capacity is reduced the patient compensates by increasing the number of breaths per minute. When this compensatory mechanism becomes inadequate, as on exercise, dyspnea is experienced. Obstructive disease, on the other hand, causes difficulty or delay in moving air in and out of the lungs. This is characteristic of conditions in which bronchospasm is a major factor such as in emphysema and bronchial asthma. Ventilation tests are most informative in these cases, particularly the forced vital capacity which shows prolongation of the expiratory phase. In granulomatous disease of the lung, such as berylliosis and the collagen processes, dyspnea results from interference with diffusion of gases across a thickened and infiltrated alveolar membrane and from a disproportion between the alveolar ventilation (V_A) and the pulmonary capillary blood flow (Q_C)—an alteration in the V_A/Q_C ratio. As a result of this disturbance the arterial oxygen saturation is lowered despite adequate ventilation.

Dyspnea generally becomes manifest when the pulmonary reserve (normally 90 per cent of the maximum breathing capacity) falls below 60 per cent. Its presence may suggest intrinsic lung disease, but it may appear in a wide variety of other conditions, such as cardiovascular disturbances, obstruction of the respiratory tract by tumors or foreign bodies and diseases of the pleura and mediastinum. Dyspnea due to a failing left ventricle must be differentiated from that due to pulmonary disease. The clinical picture of "cardiac asthma" resulting from varying degrees of pulmonary edema is typically paroxysmal and varies from slight breathlessness to acute shortness of breath. An attack may last minutes to hours and occurs frequently at night and following exertion. Loss of left ventricular reserve leads to incomplete emptying of the left side of the heart with elevation of the diastolic pressure and vascular engorgement. This produces dyspnea by decreasing lung elasticity and volume and by afferent vagal nerve stimulation. Cardiac dyspnea is mostly expiratory due to congestion and edema of the bronchial mucosa, compression of the bronchioles by engorged capillaries, and by retention of fluid in the bronchial tree. Improvement in the cardiac status will relieve the dyspnea.

In all clinical studies of pulmonary disease, dyspnea must be distinguished from hyperventilation, the phenomenon of increased but not labored breathing. This may be seen in emotional states with apprehension and sustained tension, it is usually produced by voluntary, forced deep breathing, such as during an exercise tolerance test. The increased respiratory effort "blows off" too much alveolar carbon dioxide, producing a drop in the arterial carbon dioxide tension, elevation of the blood pH and a state of respiratory alkalosis. This in turn affects the central nervous system, producing physiologic changes manifested by a sighing type of respiration, dizziness, tachycardia, numbness and tingling of the hands and face, mental apathy and even fainting.

To be considered also in the causation of dyspnea are possible psychogenic factors for the conciousness of breathing, since disturbances of respiratory rhythm are frequently part of the picture of anxiety neuroses and neurocirculatory asthenia.

Cough is a troublesome symptom present in most cases of pulmonary disease, especially when impaired function is present. It usually arises from some irritation of the respiratory mucous membrane transmitted through the ninth and tenth cranial nerves to the medulla where a special center is believed to exist. This center activates the cough reflex, which is a complex motor act involving the chest wall, diaphragm and larynx. Cough is divided into three phrases. a quick, initial filling of the lungs, then a forced expiratory effort against the closed glottis and finally a sudden opening of the glottis to allow an escape of air at high velocity. This mechanism may also be triggered outside of the respiratory tract by, for example, a foreign body in the ear, sinus infection, or even by psychogenic factors.

Cough is essentially a protective reflex, precipitated as an attempt to free the respiratory tract of irritating substances, e g , collections of bronchial secretions, foreign bodies and inflammatory products, and the products of circulatory congestion. It may be voluntary or involuntary, helpful or harmful, transitory or

chronic. Although the basic action of cough is useful, on occasion its value is lost by intensifying irritation. The tone, frequency, and precipitating influences may suggest the underlying disease In acute bronchitis the cough is usually harsh and unproductive at first, accompanied by a "raw" sensation beneath the sternum Later it becomes softer and productive of rather noncharacteristic sputum With repeated attacks, chronic bronchitis will result in a troublesome and persistent cough, which is generally worse in the morning Pressure on the trachea by an aortic aneurysm, mediastinal tumor or enlarged lymph nodes will produce a brassy cough A grunting type of cough, induced during physical effort and occurring independently of infection, suggests respiratory embarrassment. Cough observed in the asthmatic state is wheezy in type and reflects the associated bronchospasm. In suppurative disease, the cough is loose, periodic and stimulated by retention of sputum in the bronchi A persistent cough, with or without an accompanying wheeze, may be allergic in nature Pleural inflammation may produce a short, dry, painful type of cough made worse by deep breathing or change in position The cough in early tuberculosis before tissue destruction occurs is generally dry, but as caseation and necrosis occur, it becomes productive In bronchogenic carcinoma the same course of events is noted The cough is dry and irritating at first and then is accompanied by copious expectoration, often blood-streaked, especially with partial bronchial obstruction and secondary infection of the distal portion In cardiac decompensation associated with pulmonary congestion, cough may be a prominent symptom. The cough is nonproductive at first and worse at night, when the shift of fluid responsible for dyspnea and orthopnea occurs. Later, as chronic passive congestion continues, the sputum becomes frothy and blood-tinged The cough may be incessant

The presence and nature of associated expectoration should be determined, with special reference to odor and the *variations* in the amount and type as the patient changes position Tracheobronchitis, allergic states and uncomplicated emphysema are accompanied by a glary, mucoid type of expectoration Copious, foul-smelling sputum is generally seen in lung abscess and bronchiectasis. The sputum of coal miners characteristically contains large amounts of carbon particles When copious black sputum is coughed up by a miner without evidence of infection the possibility of ischemic or aseptic necrosis must be considered.

The occurrence of wheezing is important. It reflects narrowing of the bronchial lumen due to bronchospasm, edema of the mucosa, the presence of a foreign body or extraluminal pressure Although cough most often occurs in bronchial asthma with bronchospasm as the precipitating mechanism, it may occur in any of the acute or chronic inflammatory diseases of the tracheobronchial tree, the so-called bronchitides. "Asthmatic" bronchitis is a term commonly used to describe the recurrent or chronic bronchial infection associated with bronchospasm

Unilateral wheezing is most likely the result of bronchospasm, but it may reflect the presence of a bronchogenic carcinoma, a foreign body or other cause of partial bronchial obstruction such as adenoma, tuberculosis or aneurysm Differentiation is important as the therapeutic implications vary Paroxysmal nocturnal dyspnea of cardiac origin may resemble true asthma in that bronchospasm with wheezing is frequently present Wheezing in the presence of exertional dyspnea should suggest emphysema with a bronchitis rather than an allergic state.

The use of bronchodilators will relieve wheezing in most cases if the primary cause is bronchospasm When the symptom is accompanied by impairment of pulmonary function on a ventilatory basis, relief may be dramatic. The improved aeration is revealed by the increase in vital capacity and maximum breathing capacity, but more significantly in the forced vital capacity and the maximum expiratory flow rate. With relief of bronchospasm cough becomes more effective and expectoration is facilitated Thus, a clinical response may serve as an important illustration of the basic physiologic disturbance.

Hemoptysis is a frequent symptom, varying in amount from slight blood streaking to mas-

sive hemorrhage. It occurs in many known conditions but the exact cause cannot always be determined. Branches of the pulmonary and bronchial arteries in the pulmonary vein may be implicated, and in diseases such as bronchiectasis and malignancy involving the major bronchi, bleeding may originate from a ruptured bronchial artery. With ulcerative diseases such as tuberculosis, erosion of the pulmonary artery may be responsible. In all cases of suspected hemoptysis it is essential to exclude the possibility of bleeding from the throat, nose, stomach and esophagus. The significance of hemoptysis, physiologically, is the influence of extravasated blood on the patency of bronchioles

Chest pain may be significant in cases of impaired pulmonary function The character of the pain, its location and magnitude in relation to the respiratory cycle must be considered It may arise from diseases of the pleura, lungs and cardiovascular system, from changes in the mediastinum, esophagus, trachea, diaphragm, chest wall or reflexly from diseases of the abdominal organs. Care must be taken to distinguish between pain of pleural origin and that related to the intercostal muscles and the intercostal nerves. Pleural involvement produces a sharp, localized, stabbing pain, usually present on only one side, which prevents free and full breathing It is aggravated by motion such as deep breathing, bending or turning Cough produces an acute exacerbation of pain, and limiting the motion of the chest by strapping relieves it. If pain occurs during an upper respiratory tract infection associated with cough and high fever it may suggest an acute pneumonia, whereas if it occurs during the course of a chronic illness with low-grade fever, weakness, weight loss and cough, tuberculosis or neoplasm are the more likely possibilities If the pain follows an abdominal operation, especially in the presence of thrombophlebitis, pulmonary embolism must be considered Involvement of the intercostal muscles produces a constant, vague, diffuse ache, accentuated by physical movements such as deep respirations, coughing or swallowing, actions which involve the skeletal muscles; whereas a neurogenic pain tends to be sharply defined along the course of the affected nerve. Thoracic pain of skeletal origin may be identified by compression of the chest in both anteroposterior and transverse diameters, the application of pressure to all parts of the chest wall, particularly over the costochondral junctions, and percussion of the cervical and thoracic spine.

In differential diagnosis the possibility of the pain being cardiac in origin should be considered, as well as pain referred to the chest but arising in an extrathoracic organ. Pain from diaphragmatic pleurisy may be reflected to the shoulder region through the phrenic nerve.

In some cases extensive irritation of the pleura may exist without pain Use of the stethoscope may help in detection of such irritation, for pronounced friction rubs may be audible despite absence of demonstrable changes on the roentgenogram, especially if small amounts of fluid are present

Regardless of its point of origin, any painful sensation will tend to limit expansion of the affected side of the chest and in varying degrees interfere with pulmonary ventilation Relief of pain and spasm by intercostal nerve block usually permits a return of function to a more normal physiologic state The response is of value in determining the underlying disturbance of function.

Physical Examination

Physical examination, particularly of the chest, is most important in evaluating the nature and degree of impairment of pulmonary function It should be as complete as possible, with emphasis on those aspects which have a bearing on the disturbed respiratory physiology Examination should begin with an overall survey Adequate exposure of the patient is necessary. Males should be instructed to strip to the waist, and "nightingales" may be used by female patients. Note should be made of the state of nutrition, atrophic areas, deformities and injuries. The presence of bluish streaks in the skin of exposed parts of the body due to carbon deposits will suggest industrial exposure as in coal mining

The height and weight (actual and usual) should then be recorded, since these measurements will be required in the determination of

predicted values for function studies, if these are to be done. The temperature, pulse, blood pressure and respiratory rate in the resting state should be noted. A rapid pulse may suggest associated infection, an irregular pulse a cardiac factor. A rapid respiratory rate in the absence of fever generally represents hyperventilation. Note should be made of obvious dyspnea at rest and the occurrence of orthopnea. The patient should be placed in the recumbent position to note whether his breathing tolerates this position, patients with pulmonary disease usually can lie flat, whereas patients with cardiac disease are uncomfortable. The color of the fingernails and lips should then be noted. Cyanosis indicates unsaturation of the arterial blood, but no constant relation exists between the degree of unsaturation and the degree of cyanosis. Curvature of the fingernails and clubbing of the fingers may suggest chronic hypoxia, and is seen in some types of congenital heart disease, in chronic pulmonary infection such as bronchiectasis, but seldom in silicosis.

The presence of defects in the upper respiratory passages should be determined. Chronic paranasal sinus disease, deviation of the septum and chronic rhinitis will have a bearing on the ability of the respiratory tract to clear itself of foreign materials. The appearance of the chest should be noted, with special reference to deformities such as curvature of the spine and asymmetry. Note should be made of the type of breathing, whether predominantly thoracic or abdominal. Measurements of the anteroposterior diameter of the chest should be obtained at the widest and narrowest points, and also the transverse diameter at the base. The ratio may be determined by dividing the mean anteroposterior diameter by the transverse diameter. An increase in this ratio is usually significant, suggesting a tendency to the so-called barrel-shaped type of chest, a common manifestation of emphysema. A definite correlation exists between the increase in ratio and the degree of emphysema, although all degrees of emphysema may exist with all ratios.

Expansion of the chest should be observed, note being made as to whether it is free and equal or restricted on both sides or one side. The actual degree of chest expansion should be measured at the nipple line, the maximum on deep inspiration and full expiration being recorded. It is generally accepted that normal chest expansion in young adults is at least three inches. Care must be taken not to confuse a lifting type of motion with true expansion, since a definite increase in the recorded circumference may occur in both.

Percussion of the chest may disclose significant changes, but its value is limited in the presence of diffuse fibrosis or emphysema. The overdistended lung may not permit detection of underlying consolidation, particularly if the latter is centrally located. However, such abnormalities as thickened pleura, pleural effusion, pneumothorax and atelectasis can usually be detected. Hyperresonance, particularly over the upper, anterior part of the chest and at the bases, will suggest emphysema. A localized area of hyperresonance may call attention to an underlying cyst, bulla, or obstructive emphysema. Restriction of diaphragmatic motion should be studied by percussion of the lower levels of the lung on deep inspiration and expiration, the tone is less resonant as the diaphragm rises in position.

Auscultation offers valuable information. The character, intensity and quality of the breath sounds should be noted. Distant or suppressed breath sounds will suggest emphysema, although it is not uncommon to find in this condition harsh breath sounds with prolongation of both inspiration and expiration. The presence of rales is most significant. Their location and character must be determined, and whether they are exaggerated or disappear on coughing. Moist rales, however classified, generally indicate parenchymal disease, bronchiectasis or pulmonary edema. Localized moist rales over an upper lobe will suggest tuberculosis, whereas bronchiectasis should be suspected if they are basal in location. Bilateral, diffuse bubbling rales are characteristic of pulmonary edema. Musical rales suggest a bronchial abnormality, often a narrowing of the bronchus through spasm, inflammatory edema or extrinsic pressure. Generalized or scattered musical rales are found in bronchial asthma, emphysema, and in acute and chronic nonspecific bronchitis. A unilateral, localized

wheeze may suggest endobronchial obstruction by a neoplasm or foreign body. The presence of widespread musical rales may suggest the possibility of bronchospasm, and the possible use of bronchodilator drugs with inhalation therapy. The changing character of both the symptoms and the physical signs will serve as a useful guide in following the physiologic and clinical course of the illness.

Evaluation of the cardiac and circulatory status is important The presence of cardiac enlargement, alterations in the rate and rhythm, and murmurs should be noted Determination of the heart size and position by percussion may be difficult if any appreciable degree of emphysema is present. Fluoroscopic and roentgenologic examinations are far more reliable in such cases. It should be emphasized that a patient with a pulmonary disturbance may have complicating cardiac disease, either resulting from or related to it Chronic pulmonary disease, particularly emphysema, may lead to cor pulmonale and eventual right heart failure Its presence is suspected in cases with venous distention, enlarged liver and peripheral edema

Examination of the abdomen must not be neglected A protuberant, flaccid abdominal wall may be a factor in the aggravation of dyspnea, especially in cases with faulty diaphragmatic function The presence of an inguinal hernia may explain the inability to use the cough reflex effectively. The importance of these structural defects is emphasized by the effectiveness of abdominal compression obtained by using an appropriate support and hernial pad.

With completion of the physical examination, an exercise tolerance test should be given The standard test consists of 30 step-ups on a nine-inch stool. The pulse, blood pressure and respiratory rate should be recorded before, immediately after, and two minutes following exercise while the patient is lying flat in bed Note should be made as to whether the patient can do the exercise easily, whether he can just about complete it, or whether he is unable to comply. Through this means, important information may be obtained regarding cardiac and pulmonary reserve. However, interpretation of the results may be difficult, and may actually be misleading in the evaluation of pulmonary function. Failure of the pulse to return to the pre-exercise range, in the presence of marked variations in blood pressure, should suggest cardiac and circulatory embarrassment. Respiratory embarrassment is manifested by an elevated breathing rate persisting after two minutes of rest. Care should be taken to note whether a patient unable to finish the exercise does so because of dyspnea or other factors such as weakness or dizziness. A patient who voluntarily stops the step-up test because of extreme dyspnea may be considered totally disabled from this observation alone The exercise test should not be given to patients who are too disabled to exercise because of advanced age, injury, weakness, edema of the ankles or manifest pathologic conditions, particularly tuberculosis

Roentgenography

Roentgenographic examination of the chest, including both roentgenograms and fluoroscopy, is an extremely important clinical procedure for the evaluation of clinical manifestations As discussed in Chapter 35, fluoroscopy is invaluable for the study of physiologic disturbances, especially when the examiner possesses important knowledge of pulmonary physiology X-rays, particularly serial films, by providing a graphic record of disease become invaluable as a bridge between the physical examination and the physiologic laboratory.

It would appear more logical to review the roentgenogram prior to examination of the chest so that the physical examination can be pointed toward evaluation of the abnormal shadows It would be fruitless to attempt by percussion to outline a mass when the roentgenogram will more easily indicate its exact position and size, however, conversely, a pleural friction rub may be heard long before the x-ray shows evidence of a pleuritis. Serial x-rays may be more reliable in indicating the quantitative aspects of disease but the history and physical examination may be more informative from a qualitative standpoint This is particularly true in tuberculosis, where symptoms and a change

in the character of the breath sounds and/or rales may occur before demonstrable roentgenographic evidence of change is apparent. In bronchogenic carcinoma, metastasis to the mediastinal lymph nodes with an obvious superior vena caval block syndrome may be more clearly indicated clinically than by the roentgenogram

Chest x-rays should be of uniform exposure and of good technic, for differences in exposure may suggest change in a lesion. Even with the best technic, small lesions may be missed on routine scanning of an x-ray but detected on retrospective reading This is particularly true if the abnormality is behind the ribs, clavicle or heart

In addition to the routine posterior-anterior projection, a lateral exposure should be done in all cases. This will facilitate segmental location of a lesion and may suggest emphysema much earlier than if the conventional film alone were relied upon The routine x-ray is taken in deep inspiration, but it may require a film on deep expiration to demonstrate a marginal pneumothorax. A lateral decubitus x-ray may help to delineate a small pleural effusion. Body section radiography may be most helpful in the detection of cavities which may not be visible on the ordinary x-ray, and it will aid in the localization of lesions

Correlation of the Physical Examination with Pulmonary Function Studies

The nature and use of pulmonary function studies are discussed elsewhere. The various tests reveal the diverse features of disturbed pulmonary physiology and offer a quantitative measure of the degree of impairment. However, more than laboratory tests are required for complete evaluation of a disabled patient. The recognition and consideration of the many pathologic factors which contribute to the impairment of pulmonary function should be emphasized For example, disability may be related to one or more infections; metabolic, or degenerative medical conditions, such as tuberculosis, or cardiovascular disease, or conditions such as silicosis. The presence of active pulmonary tuberculosis may constitute total disability in terms of disease, but pulmonary function may not be greatly impaired. Thus, associated medical conditions must be differentiated and evaluated

Fluoroscopic Estimation of Ventilatory Function

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FLUOROSCOPY provides important information on the dynamics of breathing, especially in problems of pathophysiology that disturb normal ventilation or distribution of air in the lungs. The examination is a moving picture of the chest, showing how the diaphragm, abdominal muscles, intercostal musculature, the accessory muscles of respiration and ribs participate in the act of breathing It will reveal the differences in lucency of the two lungs and parts of each lung, and thus more clearly define the interpretations made from "still" roentgenograms Abnormal movements of the vascular hili and midline structures may give evidence of certain differences in intrapleural and intrapulmonary pressures between the two hemithoraces With reference to the hilar structures and lung markings in the lateral third of the lung field, it is possible with fluoroscopy to gain information about the status of the pulmonary vascular tree. The procedure may be invaluable in prognosticating postoperative difficulties in a particular type of surgical procedure. It is not considered as a substitute for the physiologic laboratory but, rather, another tool for exploring physical phenomena in the light of laboratory testing

The types of air-containing spaces within the lung or pleural space may be determined by using a series of simple maneuvers during fluoroscopy. The probable effect on ventilation of abnormal conditions and certain pathologic processes in the parenchyma can be estimated to a considerable extent by noting the degree of aeration and movement of the lung adjacent to such diseased areas

In attempts to teach medical residents the estimation of ventilatory function by fluoroscopy, greatest success has been achieved with those students who participated in the pulmonary function measurements in the Lung Station The best possible training (for the fluoroscopic estimation of ventilatory function) is study of the patient during laboratory investigations of pulmonary volumina, inspecting the spirograms, and using fluoroscopy prior to bronchospirometry. At the conclusion of fluoroscopy, a percentage estimation of the distribution of ventilatory function should be written in the record for comparison with the values determined by bronchospirometry After the period of training, one will find that the fluoroscopic estimations of percentage distribution of ventilatory function will seldom differ by more than 10 per cent from the values obtained by bronchospirometry However, estimation of oxygen uptake by the two lungs cannot be determined by fluoroscopy with this degree of precision In the Lung Station directed by the author, the distribution of ventilatory function is determined by fluoroscopy rather than bronchospirometry in all cases except borderline surgical risks and in certain patients with special problems requiring the measurement of oxygen uptake.

Preparation for fluoroscopic study is simple, but important Accommodation is secured by wearing red plastic goggles for thirty minutes and then sitting in total darkness for five minutes prior to the study The goggles (Willson monogoggles) may be obtained from any x-ray supply firm. Fluoroscopy should never be performed without the protection of apron and gloves If fluoroscopy is done frequently, a film badge should be worn at the top of the apron in order to detect unnecessary radiation hazard.

Fluoroscopic estimation of ventilatory function is undertaken with the patient in the standing position, whenever possible; the dorsal position is preferred to the "drooped-over" sitting posture frequently assumed by patients in a weakened condition. Patients should be naked to the waist, or they may wear a simple gown All requirements for the examination should be indicated to the patient before the room is darkened so as to avoid undue x-ray

exposure. The type of breathing is described, demonstrated and practiced. Next, the patient is asked to stand with his back flush against the x-ray table, and the fluoroscopic screen is adjusted just in front of the anterior chest. It is important to mention at this time that *the body movements* should occur easily and always under the guidance of the examiner's hand.

In fluoroscopy of the average adult, the control panel is set at 80 KV and 3 5 milliamperes Adequate observation of diaphragmatic movement *can be obtained* at 60 KV, but this may be quite unsatisfactory for the remainder of the routine study The x-ray tube should be properly *framed so that scatter over the screen* holder poses no unnecessary hazard. Whenever attention is directed from one area to the next, exposure should be interrupted, at least briefly.

After a rapid survey of both full lung fields on the fluoroscopic screen to assure normal positioning and to note the presence or absence of gross abnormalities of cardiomediastinal position, the movements of the diaphragm are studied

Functionally, there are two diaphragms, one beneath each lung In the present discussion, they will be so considered With the screen framed to include a small strip beneath each diaphragm and a slightly larger segment of lung above the diaphragms, the patient is observed during quiet breathing The patient should be asked to take deep breaths, in and out, without hesitation between inspiration and expiration After one or two such breaths, the patient is requested to breath deeply and then to blow out forcefully and rapidly During these three types of breathing each diaphragm should be observed simultaneously for range and rapidity of descent and ascent, synchronization and smoothness of motion, and to note changes in basilar lucency during inspiration and expiration

Experience will teach that some perfectly normal people do not use their *diaphragms* to any significant degree during quiet breathing When this is observed, the fact should be noted On the other hand, the patient with a high degree of expiratory obstruction, as in chronic obstructive emphysema, may exhibit a greater range of diaphragmatic motion during quiet *breathing than during forced breathing.*

Expiratory obstruction produces prolongation of diaphragmatic ascent. When obstruction is severe, *the diaphragm is immobilized during the initiation of expiration, or may* descend slightly and then rise slowly to a limited degree. With marked obstruction, there usually is an increased lucency above the diaphragm during the initial phase of expiration, evidence of expiratory trapping. Obstruction to expiration reduces the maximum breathing capacity much more than it lowers the vital capacity. If obstruction is unilateral, *or predominantly so, the observation is very important in considering the distribution* of ventilatory function.

Diffuse interstitial pulmonary fibrosis is usually recognizable in roentgenograms. The fluoroscopic picture is not striking and requires experience to recognize The entire lung fields are reduced in lucency and the estimation of intrapulmonary movement is difficult The *range* of diaphragmatic motion is reduced. *Duration* of inspiratory descent may be shortened or prolonged relative to expiration, depending on how "tight" or how noncompliant the lung has become. Duration of expiratory ascent of the diaphragms is variable but usually normal or rapid Minor degrees of pulmonary fibrosis are not recognizable fluoroscopically unless fibrosis is sharply lobar or segmental.

Prolongation of inspiratory descent of the diaphragm is an infrequent observation It is overlooked *often in patients with loss of compliance*, even during deep breathing. Both inspiratory prolongation and retardation are generally evident in the *presence of a large* intrabronchial obstruction or stenosis of one or more major bronchi.

In addition to alterations *in range and speed* of diaphragmatic motion, the synchronization of the two diaphragms is quite informative In *certain cases the phenomenon of dyskinetic* movement of one or both diaphragms may be encountered This type of movement is observed *only with deep breathing, particularly* in rapid breathing. The reason for dyskinesia is not always apparent It may be related to

Fluoroscopic Estimation of Ventilatory Function

By JOHN H. SEABURY, M.D.

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FLUOROSCOPY provides important information on the dynamics of breathing, especially in problems of pathophysiology that disturb normal ventilation or distribution of air in the lungs The examination is a moving picture of the chest, showing how the diaphragm, abdominal muscles, intercostal musculature, the accessory muscles of respiration and ribs participate in the act of breathing. It will reveal the differences in lucency of the two lungs and parts of each lung, and thus more clearly define the interpretations made from "still" roentgenograms Abnormal movements of the vascular hili and midline structures may give evidence of certain differences in intrapleural and intrapulmonary pressures between the two hemithoraces With reference to the hilar structures and lung markings in the lateral third of the lung field, it is possible with fluoroscopy to gain information about the status of the pulmonary vascular tree The procedure may be invaluable in prognosticating postoperative difficulties in a particular type of surgical procedure. It is not considered as a substitute for the physiologic laboratory but, rather, another tool for exploring physical phenomena in the light of laboratory testing

The types of air-containing spaces within the lung or pleural space may be determined by using a series of simple maneuvers during fluoroscopy The probable effect on ventilation of abnormal conditions and certain pathologic processes in the parenchyma can be estimated to a considerable extent by noting the degree of aeration and movement of the lung adjacent to such diseased areas.

In attempts to teach medical residents the estimation of ventilatory function by fluoroscopy, greatest success has been achieved with those students who participated in the pulmonary function measurements in the Lung Station. The best possible training (for the fluoroscopic estimation of ventilatory function) is study of the patient during laboratory investigations of pulmonary volumina, inspecting the spirograms, and using fluoroscopy prior to bronchospirometry. At the conclusion of fluoroscopy, a percentage estimation of the distribution of ventilatory function should be written in the record for comparison with the values determined by bronchospirometry. After the period of training, one will find that the fluoroscopic estimations of percentage distribution of ventilatory function will seldom differ by more than 10 per cent from the values obtained by bronchospirometry. However, estimation of oxygen uptake by the two lungs cannot be determined by fluoroscopy with this degree of precision In the Lung Station directed by the author, the distribution of ventilatory function is determined by fluoroscopy rather than bronchospirometry in all cases except borderline surgical risks and in certain patients with special problems requiring the measurement of oxygen uptake

Preparation for fluoroscopic study is simple, but important Accommodation is secured by wearing red plastic goggles for thirty minutes and then sitting in total darkness for five minutes prior to the study The goggles (Willson monogoggles) may be obtained from any x-ray supply firm. Fluoroscopy should never be performed without the protection of apron and gloves If fluoroscopy is done frequently, a film badge should be worn at the top of the apron in order to detect unnecessary radiation hazard.

Fluoroscopic estimation of ventilatory function is undertaken with the patient in the standing position, whenever possible; the dorsal position is preferred to the "drooped-over" sitting posture frequently assumed by patients in a weakened condition. Patients should be naked to the waist, or they may wear a *simple* gown. All requirements for the examination should be indicated to the patient before the room is darkened so as to avoid undue x-ray

exposure. The type of breathing is described, demonstrated and practiced. Next, the patient is asked to stand with his back flush against the x-ray table, and the fluoroscopic screen is adjusted just in front of the anterior chest. It is important to mention at this time that the body movements should occur easily and always under the guidance of the examiner's hand

In fluoroscopy of the average adult, the control panel is set at 80 KV and 3 5 milliamperes. Adequate observation of diaphragmatic movement can be obtained at 60 KV, but this may be quite unsatisfactory for the remainder of the routine study The x-ray tube should be properly framed so that scatter over the screen holder poses no unnecessary hazard Whenever attention is directed from one area to the next, exposure should be interrupted, at least briefly.

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